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BULLETIN OF
THE NEW YORK ACADEMY
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FEBRUARY 1939

THE SIGNIFICANCE OF THE ALBUMIN FRACTION OF SERUM

Harvey Lecture, November 17, 1938

A. Ashley Weech

Serum albumin is to be defined as that fraction of the protein of serum which remains in solution after half saturation with ammonium sulphate or which is not salted out in a 21.5 per cent solution of sodium sulphate. The fractions which are removed by these procedures are globulins. Serum albumin, so defined, possesses physiologic characteristics which are distinct from those of the globulins. It is important in maintaining the volume of the blood and it is essential to the flow of fluid across the capillary wall. These properties are intimately concerned with the general phenomenon of the circulation of the blood, a circumstance which makes it peculiarly appropriate that they be discussed before the Harvey Society. Moreover, the physiologic properties of serum albumin are of great importance in medicine for the amount of albumin which circulates in the plasma is easily depleted when health is disordered. An understanding of this process of depletion, and its converse, replenishment, is essential to correct appraisal of the significance of the albumin fraction of serum.

In selecting material in a large field from which to prepare this eve-

ning's lecture, I have perforce given preference to investigations which have occupied the attention of workers in the laboratory which I represent. A few aspects only can be included of the important role of serum albumin in regulating the distribution of fluid between capillaries and tissue spaces; this phase of the subject has been covered in a recent Harvey Lecture by Eugene M. Landis.[1] Likewise, Cecil K. Drinker[2] has brought before you some of the problems which require elucidation in connection with the occurrence of serum proteins in lymph and I shall not enter this field of controversy. Since familiarity with ground to be covered will aid in orientation, I shall begin by presenting an outline:

Part I. Effect of diet on serum albumin concentration
- a. The process of depletion
- b. The process of replenishment

Part II. Physiologic importance of serum albumin
- a. Fluid distribution and edema
- b. Absolute and relative permeability of capillaries
- c. Regulation of blood volume

Part III. Medical control of serum albumin deficiency
- a. Injection of acacia; transfusions with serum and blood
- b. Diet; qualitative differences among food proteins in promoting albumin synthesis

Part I.

In 1929 Frisch, Mendel, and Peters[3] reported that young rats fed on diets composed chiefly of carrots developed deficits in serum protein. The diet was deficient in protein, but otherwise adequate. In 1931 Shelburne and Egloff[4] described the development of hypoproteinemia in a dog during maintenance on a low protein diet. These observations have been used in the laboratory of the Babies Hospital to provide a method[5, 6] for depleting the serum albumin. Our story can be opened by observing the method.

Dogs are maintained on a low protein diet, the composition of which is indicated in Table I. The quantities listed are the amounts given to each dog per day. Animals subsisting on the diet have always exhibited a negative balance of nitrogen. Metabolism observations indicate an average daily loss of nitrogen of 1.15 gm. The biological effects of subsistence on the diet appear to be referable to deficiency of protein alone. When the diet is supplemented with casein it has proved adequate for maintenance

of health. The addition of extra amounts of various vitamins[7] has not altered the course of experiments.

TABLE I

COMPOSITION OF LOW PROTEIN DIET

	grams
Carrots	300
Rice	35
Lard	40
Cod liver oil	10
Sugar	115
Salt mixture	5
Water, sufficient to make	900

Furnishes 1200 calories; 1.23 gm. nitrogen

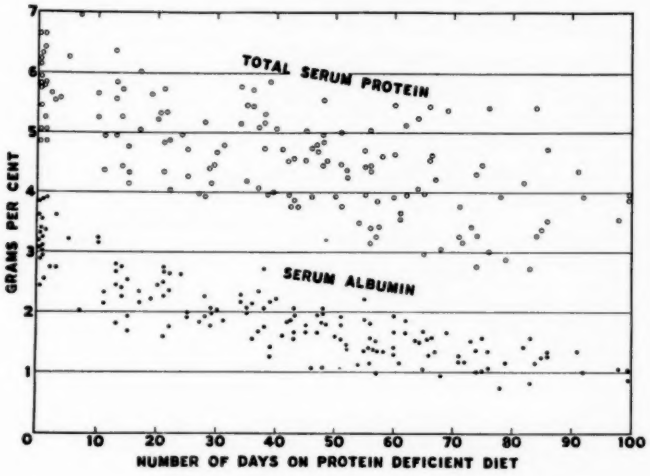

Chart 1—Concentration of albumin and total protein in the serum during maintenance on the low protein diet. From the *Journal of Experimental Medicine.*[6]

Chart 1 shows the results of 150 determinations of the albumin and total protein of serum in twenty-one dogs during maintenance on the diet. The downward trend of albumin and total protein with continuance of the diet is pictured clearly. In Chart 2 the trends are shown by average lines and the course of the globulin fraction is depicted. The average concentration of globulin remains singularly constant; it follows that the fall in total protein is brought about entirely by depletion of the albumin fraction.

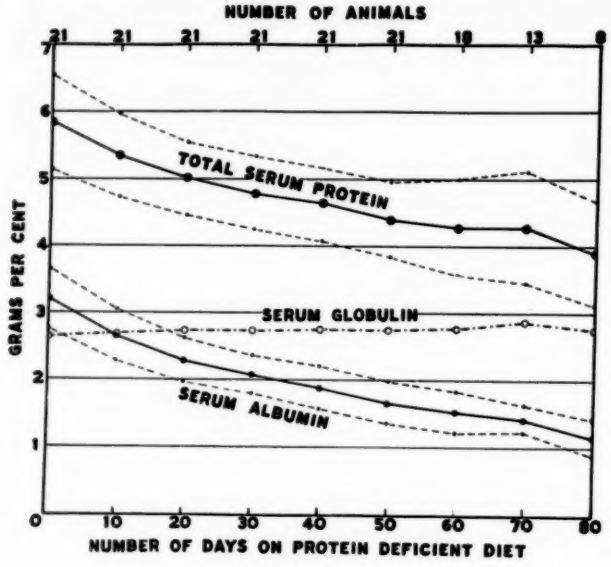
NUMBER OF ANIMALS
21 21 21 21 21 21 18 13 8
GRAMS PER CENT
TOTAL SERUM PROTEIN
SERUM GLOBULIN
SERUM ALBUMIN
0 1 2 3 4 5 6 7
0 10 20 30 40 50 60 70 80
NUMBER OF DAYS ON PROTEIN DEFICIENT DIET

Chart 2—The average trends of albumin, globulin, and total protein during maintenance on the low protein diet. The dotted lines above and below the unbroken lines for albumin and total protein are placed at a distance of one standard deviation from the average values. From the *Journal of Experimental Medicine.*[6]

There are two additional points concerning the depletion of albumin. The first can be seen from the chart, namely, that the rate of decline is more rapid during the initial days or few weeks of maintenance on the diet than subsequently. On the average it requires eleven weeks to double the fall in concentration which develops in three weeks. The slowing in the rate of decline with the passage of time has been shown in metabolism studies to be associated with a progressive diminution in the nitrogen lost by the body. There is thus portrayed an adaptive ability of the body in adjusting its metabolic processes so as to spare protein. A similar adaptive ability has been described in humans[8] during subsistence on low protein diets and the process has been shown to be associated with a fall in the basal output of energy.[9, 10]

A second and curious fact concerning the depletion of albumin is that

the rate of fall is independent or almost independent of the amount of energy consumed in the diet. One might well have expected that a high intake of calories in the form of carbohydrate and fat would not only protect the body nitrogen but also slow to a minimum the depletion of protein in the serum. This does not appear to be the case. We have not been able to discern that the decline is more rapid during fasting than when the energy intake is liberal. Among eighty-three animals in which the daily dietary calories varied from fifty to eighty-seven per kilo of weight, the coefficient of correlation between energy intake and percentage albumin depletion after three weeks was only 0.11, a degree of association entirely devoid of statistical significance.

We have now seen that the simple procedure of maintaining a dog on a low protein diet not only allows the production of serum albumin deficits in a laboratory animal and thereby affords the means for observation of the consequences but also that some features which characterize the process of depletion can be made out. It will be instructive to watch the process in reverse so as to learn something of the nature of regeneration.

In the first group of experiments[11] moderate albumin depletion was obtained by administering the low protein diet to four dogs for a period of three weeks; the diet was then supplemented by the addition of beef so that each animal would receive eighty calories and 5 gm. protein per kilo. The degree of albumin depletion can be seen in Table II by comparing the initial levels in the first column with the levels in the second column which represent analyses at the end of the depletion period. Subsequent daily levels when the diet was supplemented with beef are shown in the remaining columns. The result was the same in each of the four experiments; it can be visualized best by a graph, Chart 3, showing the average course of regeneration. The course can be described with close approximation by a straight line. In two of the four experiments the regeneration was followed until the albumin had attained its previous level of health. Within the limits of experimental error there was no break in the straight line path of albumin concentration until this level was reached. Thereafter, no further regeneration occurred. These experiments are informative because they dispose of an idea which has been expressed or implied in recent literature, namely, that the strength of the stimulus for regeneration of albumin is proportional to the degree of albumin depletion. Apparently the stimulus is constant so long as any de-

TABLE II

Dog	Before Depletion	Days on Regeneration Diet 0	1	2	3	4	5	6	7	8	9	10	11	12
7-31	3.65	2.82	3.17	2.97	2.99	3.28	3.28	3.65	3.52	3.64	3.63		3.61	3.64
5-31	4.22	3.08	3.04	3.13	3.42	3.50	3.68	3.93	4.10	4.12	4.18	4.11	4.30	4.24
8-04	3.57	2.56	2.58	2.71	2.79	2.81	2.83	2.94	2.88	3.12	3.18	3.14		3.26
9-51	3.98	2.96	3.06	3.09	3.26	3.32	3.31	3.58	3.53	3.60	3.75			
Average	3.86	2.86	2.96	2.98	3.12	3.23	3.28	3.53	3.51	3.62	3.69			

Results of daily determinations of serum albumin concentration during regeneration on a diet which furnished 5 grams of protein per kilo. The added protein was in the form of beef muscle (chuck). The figures refer to grams per 100 cc. serum. From the *Bulletin of the Johns Hopkins Hospital.*[11]

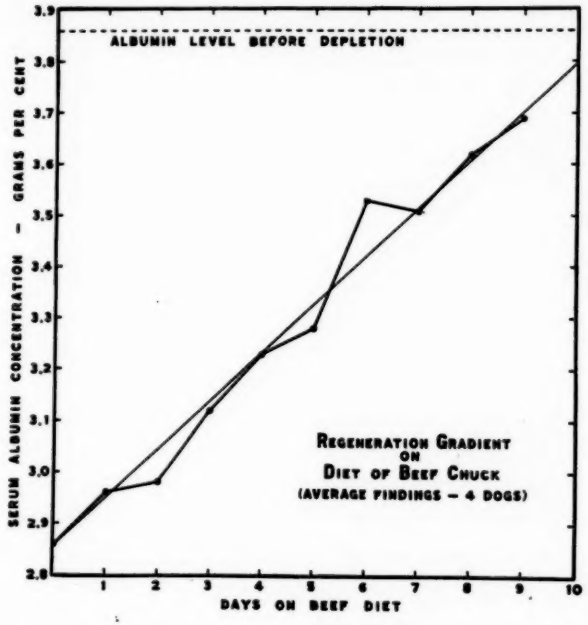

Chart 3—From the *Bulletin of the Johns Hopkins Hospital.*[11]

pletion exists. When the intake of food is constant, a fixed amount of the diet will be utilized each day for fabrication of albumin. The experiments are further informative because the result can be contrasted with the type of regeneration which occurs under other conditions, conditions in which we incline to the opinion that the body mechanism responsible for synthesizing albumin has been impaired. From this point of view the straight line regeneration curve can be regarded as exemplary of the type of regeneration to be expected when the mechanism for forming albumin is normal.

Within recent years the accumulation of clinical evidence has shown that chronic depletion of the serum albumin is apt to be associated with disease of the liver. In 1932 Thompson, Ziegler, and McQuarrie[12] reported a case of hypo-albuminemia and chronic edema in a girl, aged two and one-half years, who failed to exhibit a rise in serum albumin or alleviation from edema when given a diet upon which the nitrogen balance was positive. Since there was no loss of albumin in the urine to explain

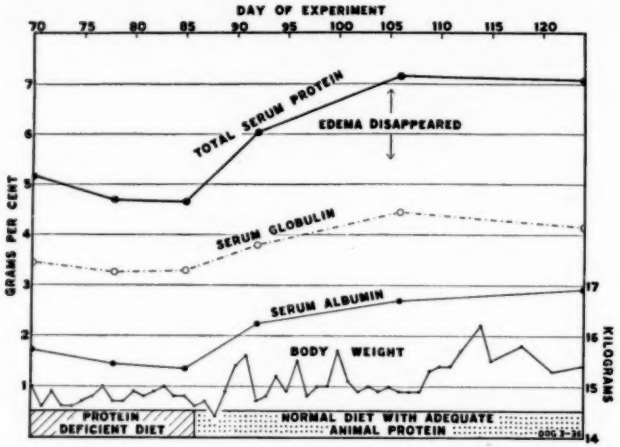

Chart 4—The regeneration of serum albumin in a dog debilitated by prolonged subsistence on the low protein diet. Before depletion the albumin concentration was 3.9 gm. per cent. The lowest level was 1.4 gm. per cent on the eighty-fifth day. After thirty-eight days of adequate feeding it had risen to 2.9 gm. per cent. From the *Journal of Experimental Medicine*.[6]

the serum deficit, the authors suspected a defect in the body in the process of manufacturing serum protein. In a later communication,[13] 1936, after the patient had come to autopsy, it was reported that she had suffered from primary atrophy of the liver. In 1933 a similar case was described by Myers and Taylor;[14] in this patient liver injury was suggested by the results of tests of liver function. In 1935 Myers and Keefer[15] discussed the relationship between depleted serum protein and cirrhosis of the liver; they explained the low serum protein as being the result of alteration in the function of the liver. The writer[16] has cited the case of an infant in whom low serum albumin and edema were apparently caused by syphilis which involved the liver extensively. Such circumstances make it relevant to inquire concerning the status of this function of the liver in other types of hypo-albuminemia, namely, in the types found in nephrosis and in chronic malnutrition.

That the mechanism for forming albumin may be impaired by prolonged malnutrition is suggested by several of our experiments with

dogs.[6, 11] When the time of maintenance on the low protein diet is lengthened to cover a period of several months, health and vitality are affected markedly, and replenishment of the albumin deficit is sometimes a protracted and difficult process. This state of affairs is illustrated by the experiment outlined in Chart 4. With this animal after eighty-five days on the low protein diet the albumin had fallen from 3.9 to 1.4 gm. per cent; the appetite had failed, vitality was low, and it seemed that life could not continue for more than a few days. From this time on an adequate and varied diet was offered daily; because of anorexia small amounts only were eaten at first and life was sustained by gavages of milk. A detailed record was not kept of the amount of food consumed daily but it is clear that the intake of both protein and energy increased slowly as strength and health returned. The behavior of the serum albumin concerns us here. During the first week the rise in concentration was rapid from 1.4 to 2.3 gm. per cent; during the next two weeks the rise to 2.7 gm. per cent was much slower; after three more weeks a level of only 2.9 gm. per cent had been attained. Thereafter, the gains continued but were extremely slow. After six months a level of 4.0 gm. per cent had been reached which was slightly above the previous concentration of health. With this animal, after an initial rapid response to food, subsequent albumin regeneration was slow and apparently independent of the quantity of food consumed. The form of the regeneration curve is impressively different from the straight line found in animals after short periods of depletion when health and vitality are not obviously impaired. The slow approach to normal suggests that replenishment is being delayed pending restoration to normal of the organ concerned in the synthesis of albumin.

If one accepts for the moment the possibility that liver injury was responsible for the delayed replenishment of albumin in this experiment, it is important to note that the injury was one which did not affect the early rate of synthesis but rather that it fixed at a subnormal value the level which could be reached. This observation may have considerable clinical significance. The constant low levels of albumin in patients with cirrhosis of the liver are similar; in such cases the initial response to an improvement in the diet is often meager, and complete recovery does not take place because the liver damage is permanent. In many cases of nutritional edema in humans, there is found upon institution of adequate feeding the same initially rapid and subsequently slow regeneration of

albumin as in our experiments with dogs. Such regeneration curves suggest that the synthesis of albumin may be impaired in man as in the dog by prolonged malnutrition. In the form of Bright's disease called "nephrosis," it has been customary to regard the extremely low levels of albumin in the serum as due entirely to loss of albumin in the urine. That defective synthesis of albumin may also play a part in maintaining the depletion is suggested by the constant nature of the albumin level in the serum in some patients over long periods when protein intake and degree of albuminuria are varying widely. In one of the cases reported by Keutmann and Bassett,[17] observations are recorded over a period of seven months during which the patient always received an adequate caloric intake. However, the diet was changed from time to time to include a number of food proteins at levels which varied from 68 to 180 grams per day. To a certain extent increases in dietary protein were associated with greater loss of protein in the urine; nevertheless, the higher intakes also produced significantly greater storage of nitrogen in the body. Under the circumstances it is noteworthy that during the entire seven months the concentration of protein in the serum remained almost constant at a level near 3.9 gm. per cent. Such constancy of serum protein concentration is difficult to understand in terms of defective kidney function alone. However, it is not difficult to explain if one admits the possibility of defective albumin synthesis of a type similar to that observed in our experiments with dogs.

In summary of Part I of this presentation: The administration of a low protein diet to a dog results in a progressive decrease in the concentration of albumin in the serum; the decline is at first rapid, later more gradual. A return to adequate feeding is followed by regeneration of the albumin. When the period of depletion has been short and the vitality of the animal is not impaired, the regeneration is rapid and on a constant diet follows a path of equal daily increments until the concentration of health has been regained. After long and debilitating periods of depletion, the regeneration, although initially rapid, is subsequently retarded and approaches the concentration of health very slowly. It has been suggested that the delayed type of regeneration may result from injury of the mechanism concerned in synthesizing albumin, a mechanism presumably located in the liver. Finally, data have been presented which intimate the existence of similar phenomena in several types of disease in humans.

Part II.

Your attention must now be turned to the importance in physiology of the albumin fraction of serum. I have already stated that it is not necessary to discuss fully the role of albumin in the control of fluid distribution at the capillary boundary since a number of aspects of this subject were covered in a previous Harvey Lecture. We may, however, record with pride that a New York physician, Epstein,[18] was the first to suggest that hypoproteinemia is the direct cause of edema in nephrosis and, we should fail to give honor where honor is due if we did not mention the great physiologist, Starling,[19] who first perceived the importance of the osmotic pressure of the protein of serum in preventing the passage of the fluids of plasma across the wall of the capillary into the tissues. It is interesting, however, that general acceptance of the postulates of Starling did not occur until Leiter,[20] 1928, and Barker and Kirk,[21] 1930, demonstrated that edema could be produced in otherwise healthy dogs by plasmapheresis, a mechanical method for removing plasma protein rapidly from the circulation.

That a correlation exists between the level of serum albumin and certain types of edema is now firmly established. With nephritic patients Moore and Van Slyke[22] found that an albumin concentration below 2.5 ± 0.2 gm. per cent was usually associated with edema. In malnutrition Bruckman and Peters[23] reported that edema almost always develops when the albumin falls below 3 per cent. In a study of nutritional edema in China,[24] dropsy was not observed when the albumin was greater than 3.0 per cent and was generally present when the level was less than 2.5 per cent. The relationship between albumin and edema in the experimental edema of dogs[25] is shown in Chart 5. The black dots represent analyses of plasma made when edema was present and the open circles refer to estimations before edema had developed or in a few instances after it had disappeared. Edema rarely appeared before the albumin was below 2 per cent; it was more often present than absent when the albumin was between 1 and 2 per cent; below 1 per cent edema was always present. Between globulin and edema no correlation can be discerned and the slight correlation in the total protein column obviously results from the albumin component.

The effectiveness of serum albumin in preventing edema depends upon its osmotic pressure. This pressure is exerted across the wall of the

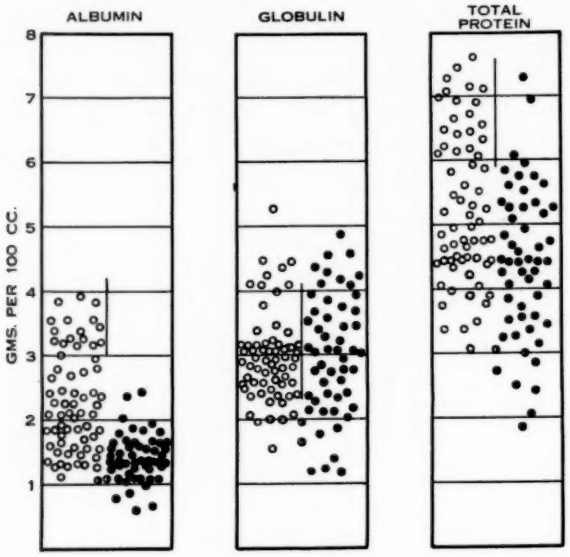

Chart 5—The relation between plasma protein concentration and edema in dogs. Open circles indicate estimations when no edema was present; black circles refer to determinations when edema was present; vertical lines in the middle of each column indicate the range of normal variation. From the *Journal of Clinical Investigation.*[5]

capillary because the capillary membrane is relatively impermeable to plasma protein while at the same time it is freely permeable to water, electrolytes, and other dissolved substances of low molecular weight. Under conditions where the capillary wall is damaged, the impermeability is destroyed and the edema which results represents simply the passage of plasma into the tissue spaces. Such forms of edema result from allergy and from inflammation. They need not concern us here. We must, however, be interested in the extent to which this protein traverses the wall of the capillary when there is no gross injury, that is, in defining as accurately as possible what we have called "relative impermeability." The available evidence is drawn from determinations of total protein in lymph[26,27] and in edema fluid. In view of Cecil Drinker's lecture[2] before this Society less than a year ago, I shall not discuss the subject of protein

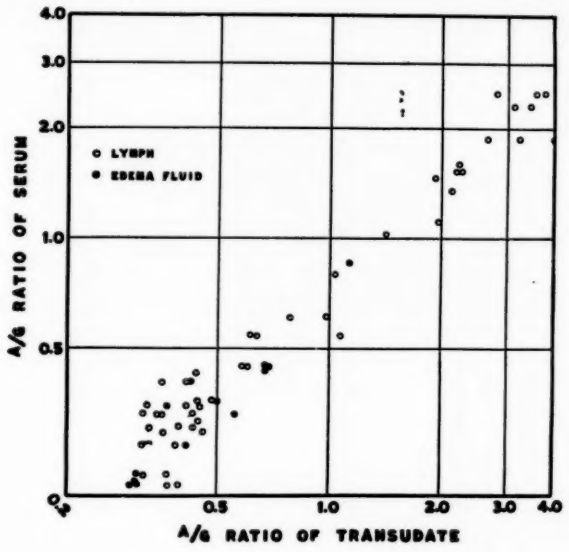

Chart 6—The relationship between the albumin: globulin ratios of concurrently collected samples of serum and transudate. A logarithmic scale has been used to avoid crowding of the data in the lower left-hand corner of chart.

in lymph. Much information concerning the protein in edema fluid has been assembled by Peters.[28] In nephrosis the fluid contains very little protein, usually less than 0.1 gm. per cent; in edema from myocardial failure the fluid contains more, generally from 0.5 to 2.0 gm. per cent. With nutritional edema in man, data assembled in our laboratory[16] indicate that the protein content of subcutaneous edema fluid varies from 0.1 to 0.6 gm. per cent. With experimental edema in dogs our experience is more extensive;[25] thirty samples from fourteen dogs have been examined. The range of protein concentration was from 0.02 to 0.72 gm. per cent; the average level was 0.23 gm. per cent and the median level was 0.17 gm. per cent.

The data just cited are of great value in tracing the behavior of total protein in plasma as it flows through the capillaries; they do not help specifically in following the course of the albumin fraction. It has been suggested that albumin because of its smaller molecular size may diffuse

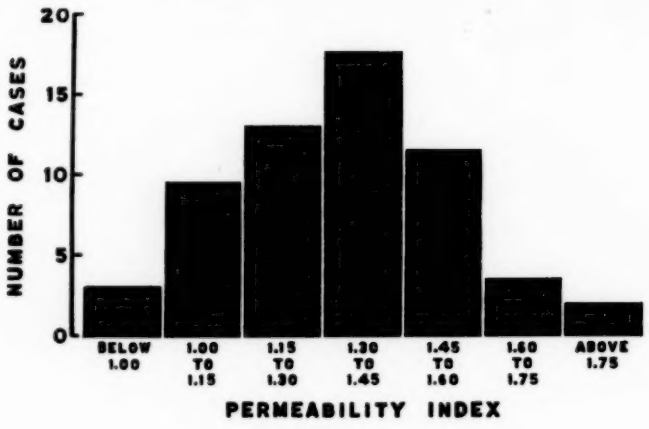

Chart 7

through the capillaries more freely than globulin and that the bulk of protein in edema fluid may be albumin. Because the osmotic pressure of albumin is much greater than that of globulin, it is desirable to have positive knowledge concerning the relative amounts of albumin and globulin in edema fluid. Information on this point has been supplied by Goettsch who in association with Kendall[29] developed a method for fractionating the serum proteins accurately in fluid samples of low protein content. The method is an outgrowth of fundamental work of Heidelberger and Kendall[30] and depends upon the precipitin reaction which appears when such fluids are brought into contact with specific rabbit antisera. Twelve samples of subcutaneous edema fluid and forty-eight samples of lymph from the extremities were obtained from normal and edematous dogs for this study; serum collected concurrently was also analyzed. Chart 6, prepared from these analyses, shows that the albumin: globulin ratio of a transudate is related closely to the albumin: globulin ratio of its corresponding serum. The concept is strongly supported that the albumin and globulin of lymph and edema fluid originate by filtration from the plasma. Incidentally it is shown that lymph and edema fluid are similar in this respect. In Chart 7 we have calculated for each transudate what may be called a "permeability index" and the indices have been arranged in the form of a frequency polygon. The index is secured when the A:G ratio of the transudate is divided by the A:G ratio of

the serum. When the permeability of the capillary is the same for albumin as it is for globulin, the index will have a value of one. As the index rises above unity a correspondingly greater differential permeability in favor of the smaller albumin molecule is indicated. The chart shows essentially a normal type of distribution for these permeability indices. The mode lies between 1.30 and 1.45; the average index is 1.35. The result tells us that albumin does traverse the capillary more readily than globulin but the difference is not extreme; if the ratio of albumin to globulin in serum is known the ratio in the transudate can be estimated by multiplying by 1.35. The chart shows three instances out of sixty in which the permeability index was less than one. I shall not attempt to explain these values other than to state that the figures were close to unity and that the slightly lower results may be merely an expression of analytical difficulties. They scarcely constitute grounds for believing that protein crosses the capillary wall by any other process than that of simple filtration.

Data of a similar nature for humans with edema are still meager. In seven cases where satisfactory analysis was possible the permeability indices ranged from 1.24 to 2.29 and averaged 1.55. There is little to suggest that in this respect the capillaries of the human do not behave like those of the dog. The reason why a larger number of analyses in the human is not available is part of another story which because of its importance can be touched on here. At the Babies Hospital most of the patients from whom adequate samples of edema fluid can be secured are children with nephrosis. It was while attempting to analyze samples from such patients that Dr. Goettsch[31] was led to discover that not only is the serum protein depleted in nephrosis but also that a part of the remaining protein is altered in a way which can be detected by the precipitin technic. This fact must become important in our ultimate understanding of the pathogenesis of nephrosis.

In addition to the data in Chart 7, three permeability indices have been determined for dog ascitic fluid. The values are 1.82, 1.98, and 2.18, all appreciably higher than the modal index for subcutaneous edema fluid and lymph. It will be recalled that fluid which leaves the blood to enter the subcutaneous tissue spaces must pass only one filtering layer of capillary endothelium; that which enters the abdominal cavity must in addition traverse the peritoneum. This fact may account for the higher indices recorded for ascitic fluid. If we suppose that capillary and peri-

toneum exert the same differential effect on filtration, a permeability index of 1.82 can be calculated for the two surfaces combined. The average of the three determined indices is 1.99.

I must now request a shift in the direction of your attention in order that we may consider another property of serum albumin, namely, that property which concerns its role in maintaining the volume of the blood. Not so many years ago the low concentration of protein in the serum of patients with nephrosis was interpreted to mean that both blood and tissues shared in the accumulation of edema; there was much talk of so-called "hydremic plethora." Probably Darrow,[32] 1926, was the first to record actual measurements which led to the conclusion that blood volume and plasma volume are below normal during the edematous stage of this disease. In view of contemporaneous work it is of interest that Darrow was able to reach his conclusion not on the basis of single measurements during the edematous phase but because volumes during edema and sometime after the disappearance of edema were compared. Other investigators[33] who studied the problem during this period, although able to dispose of the older concept of hydremic plethora, did not perceive the actual lowering in blood and plasma volumes. The findings of Darrow in nephrosis were later corroborated by Waterfield.[34] In 1932 Chang[35] in China in studying patients with nutritional edema found a close parallelism between blood volume and plasma protein. About the same time Lepore[36] made observations on dogs in the anemia colony of Whipple in Rochester; he found that the volume of the plasma varied consistently with changes in the concentration of albumin in the serum. Later, 1936, Melnick and Cowgill[37] reported that the parallelism between change in plasma volume and change in serum protein could be disturbed by significant alteration in the volume of red cells. You will see that we had been led to a similar conclusion.[38]

Chart 8 shows the average volume findings in ten of our dogs during maintenance on the low protein diet. Along with the decline in albumin which has already been described there is seen here to be a progressive fall in the total volume of the blood. The decline in red cell volume is likewise continuous but the plasma volume decreases for from twenty to thirty days only and thereafter remains at an approximately constant level. The failure of plasma volume to continue to fall does not mean that at this stage it is no longer sensitive to change in albumin concentration. In other experiments we have shown that at any degree of albumin

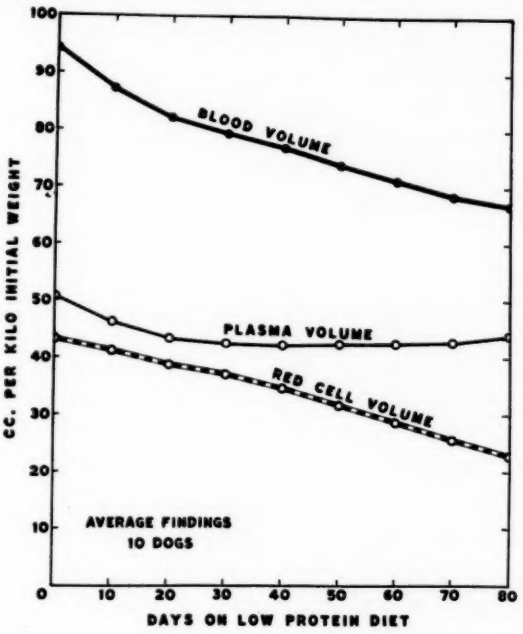

Chart 8—Changes in blood volume, plasma volume, and red cell volume during maintenance on the low protein diet. From the *Journal of Clinical Investigation*.[38]

depletion there will be an immediate rise in plasma volume if the albumin concentration is raised by transfusion either with serum or with solutions of serum albumin. We can imagine, however, that the continuous fall in blood volume which results from diminishing red cells has brought into play an opposing force strong enough to resist the effect of decreasing albumin concentration on plasma volume.

The fact that change in albumin concentration exerts an effect on the volume of the plasma assumes considerable importance when conditions are such that albumin is either rising or falling and it is desired to draw conclusions concerning some circulating substance from serial measurements of its concentration in blood. In Chart 8 it is seen that for some days the rate of decline is more rapid for plasma volume than

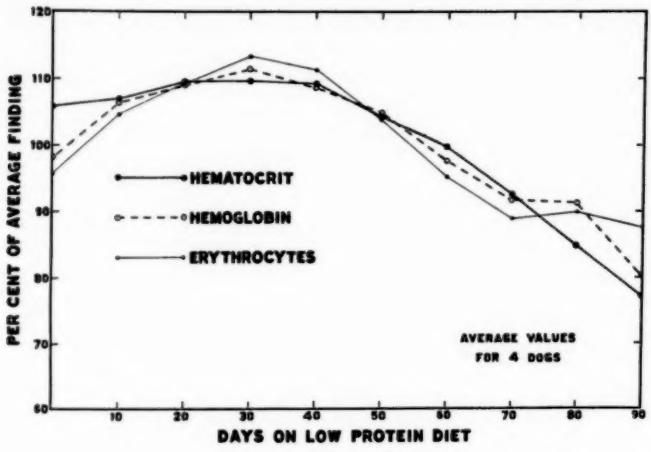

Chart 9—Variations in per cent cell volume, hemoglobin concentration, and number of erythrocytes during maintenance on the low protein diet. From the *Journal of Clinical Investigation.*[38]

for cell volume. During this period then the concentration of red cells must rise even though the total quantity is falling. This paradox is brought out in Chart 9 which presents the usual type of hemoglobin, erythrocyte, and hematocrit measurements in four dogs during maintenance on the deficient diet. If such measurements only were available one might be led to the curious and incorrect conclusion that ingestion of a deficient diet has a temporarily beneficial effect on hemoglobin and erythrocytes. I may add that examples of the fallacy of such reasoning are easily found in the clinical records of patients for even as illness and anorexia tend to go hand in hand so also does failure of appetite associate itself with a fall in serum albumin.

Part III.

The physician who investigates disease need feel no shame if his labor brings understanding even though there be no relief for his patient. Nevertheless, he must ultimately be impelled by at least a desire to strengthen the armaments of therapy. With this thought in mind I shall now turn to a consideration of measures which are being devised to re-

lieve the symptoms of albumin depletion. Of such symptoms the most conspicuous is dropsy. It is therefore fitting that we should consider first the attempts to remove edema by injecting into the circulation either albumin, as contained in serum or blood, or a substitute for albumin, like gum acacia. As a preliminary caution, however, we should be reminded that the phenomenon of diuresis is complicated and that it depends more directly upon renal activity than upon any particular distribution of fluid between circulation and tissues. A complete explanation of the initiation of diuresis is therefore not given when we say that this or that procedure has raised the colloid osmotic pressure of the blood. Indeed, we are forced to this conclusion by the observation that diuresis with elimination of edema occurs not infrequently when no evidence can be found that the osmotic pressure of the protein in the circulation has been altered. In such cases slight rises in albumin concentration in the plasma are often better interpreted as signs of blood concentration resulting from the diuresis than as the cause of its inception. In this connection I should like you to entertain a thought concerning the possible sequence of events when transfusions with serum, with blood, or with acacia are successful in initiating a diuresis. Experience indicates that these procedures, even when successful, usually produce slight and sometimes negligible effects on osmotic pressure. The evidence is strong, however, for an abrupt rise in plasma volume. It may well be that the rise in plasma volume is associated with an increase in renal blood flow and that the latter is responsible for stimulating kidney activity. In any case the possibility that some such sequence of events is involved will help in our understanding of observations that have been made in the clinic and in the laboratory.

Transfusions with blood to replenish the serum albumin have been attempted in many places. I know of no tabulation which permits appraisal of the efficacy of the procedure. Reports have appeared of cases in which the measure was successful in initiating diuresis but failure to obtain such action is a more common experience. Transfusions with serum alone have undoubtedly been used from time to time even as we at the Babies Hospital have occasionally turned to this procedure. Reports indicating conspicuous success have not appeared. Probably because the method involves the labor of handling large volumes of blood and because in many instances the blood must be purchased, the attention of investigators has been directed along other lines.

In 1932 Hartmann and his colleagues[39] in St. Louis suggested the use of acacia as a substitute for serum albumin in raising the osmotic pressure of plasma. By injecting this gum in large amounts intravenously Hartmann was successful in initiating diuresis in five out of six patients with nephrosis. Our own experience with this procedure has not been so rewarding; because severe constitutional reactions were encountered in the first few patients, we have not encouraged its use. Moreover, it has been reported[40] that much of the injected acacia is ultimately deposited in organs throughout the body, particularly in the liver, and Dick and his associates[41] have observed clinically that the continued use of acacia depresses still further the already depleted serum protein and is associated with an enlarged tender liver. Under such circumstances it is probably fair to assume that the procedure will not become popular even though its occasional use may be justified.

During the past summer a report has appeared of a more promising method of combatting serum albumin deficiency. Aldrich, Stokes, and other associates[42] have described a diuretic effect in nephrosis from injections of concentrated human blood serum. The serum used had been preserved in dried form by the lyophile process and was injected after redissolving so as to yield fourfold or fivefold concentration. In six of nine patients treatment was followed by complete and immediate diuresis. The authors did not feel, and indeed their analyses scarcely indicate, that the favorable results were due entirely to the osmotic action of the lyophile serum. They suggested that in addition some substance had been supplied which set off the patients' own mechanism of diuresis. Systemic reactions to the serum were usually mild but in two instances chills and high fever were seen. Dr. Lyttle has had some experience with this procedure at the Babies Hospital. Four children with nephrosis have been treated and in two of these the more severe type of reaction with chills and fever was noted. In only one case was satisfactory diuresis elicited. We were likewise led to conclude that the effect could not be ascribed to elevation of serum albumin concentration, but a sharp fall in the hematocrit reading following each injection suggested that the procedure did increase the plasma volume.

Because this form of treatment is destined to receive extensive trial in the near future it may be helpful to review one of a series of experiments performed several years ago[43] in which nutritional edema in the dog was treated by a similar method. Dog 2-07, Chart 10, had received

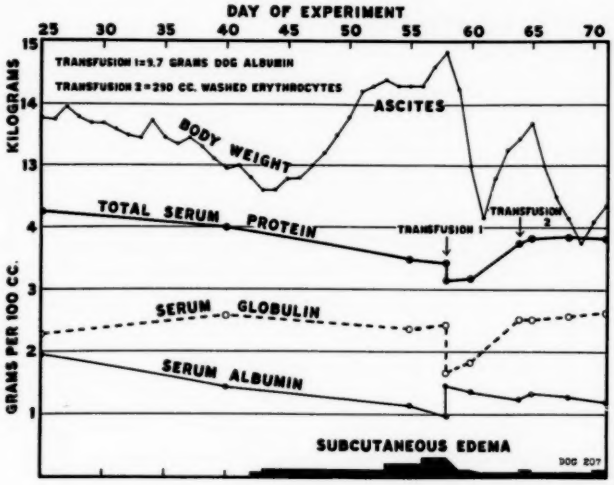

Chart 10—The effect of transfusion on serum proteins and edema in nutritional edema in a dog.

the low protein diet for fifty-eight days before treatment by transfusion was tried. The serum albumin had declined to less than 1 per cent and ascites had developed. At this point the animal was given intravenously 38 cc. of a 25.4 per cent solution of dog serum albumin. Before injection the plasma volume was measured and the total albumin in the circulation estimated to be 6.3 gm. The amount of albumin injected was 9.7 gm. The reaction was mild but similar in type to that observed in other dogs which have exhibited chills, diarrhea, and rapid irregular pulse of low volume. The subsequent clinical effect of diuresis which continued for three days was most encouraging. The changes in serum protein concentration are shown on the chart, a rise in albumin of only 0.5 gm. per cent and a fall in globulin great enough to produce an actual lowering in total protein. These changes were associated with a sharp fall in the hematocrit reading. Separate calculations based both upon the fall in hematocrit and upon the alteration in albumin indicate that the transfusion was followed by an abrupt increase in plasma volume from 630 to about 1,080 cc. We suspect that the reaction of shock may depend upon the sudden demand on cardiac reserve consequent upon such in-

creases in blood volume. The change in protein concentration in the serum is scarcely an adequate explanation for the degree of diuresis which ensued. Some light may be shed on this point by subsequent events. After the three-day diuresis the body weight again rose as edema reaccumulated. On the sixty-fifth day a second transfusion was given with 290 cc. of erythrocytes which had been washed in saline to remove the plasma. This time there was no untoward reaction and no demonstrable change in the serum proteins. Nevertheless, diuresis which lasted for four days was again instituted. The large volume of transfused red cells must have increased the total blood volume and this circumstance may have stimulated the kidney to diuresis.

If any conclusion is to be drawn from experiments of this type, it is that red cells and serum may both have some value in treatment. Transfusions with serum are invariably followed by a fall in relative cell volume and it would seem the part of wisdom to administer enough whole blood to prevent the fall. If it is true that untoward reactions may result from sudden increase in plasma volume, small and frequently repeated, rather than large, transfusions are indicated.

The futility of attempting to transfuse enough serum to replenish entirely the deficits in disease has been impressed on all who have tried the procedure. Albumin depletion is invariably a sign that the stores of nitrogen in many tissues are likewise depleted and it may be impossible to prevent an exchange of protein between circulation and other tissues when large volumes of serum are injected. Whipple and his associates[44] have already indicated the possibility of such an exchange by demonstrating in the dog that the protein requirement of the entire body can be met by massive transfusions of plasma. The only practical way in the clinic of meeting the full demand of the body for protein is through the diet.

From time to time and in different places the idea has evolved that some dietary proteins may be more efficient than others in supplying the needs of the plasma. There is opportunity merely to mention the convincing and provocative work of Whipple[45] who with his associates has utilized the technic of plasmapheresis to show that qualitative differences exist among different foods with respect to their utilization in forming serum protein. The remaining portion of this lecture must be devoted to experiments having a similar purpose now under way in our own laboratory.[11, 46] These experiments have as their ultimate goal the

classification of the more important food proteins with respect to their ability to promote the formation of serum albumin.

The method which is being used to assay the food proteins is simple. A healthy dog is selected and placed under daily observation for six days on a standard diet of adequate protein content. The standard diet is a mixture of 900 grams of our basal low protein ration with 90 grams of casein. The concentration of albumin in the serum is then measured; the casein is removed from the diet and the period of depletion of the serum albumin is begun. After three weeks the serum albumin is again determined and the period of regeneration started on a diet composed of a mixture of the basal diet and the food protein to be tested. The mixture is fed at an energy level of eighty calories per kilo and at a protein level of 2.5 grams per kilo. After one week on this diet the final measurement of serum albumin concentration is made.

The initial albumin analysis is a control determination only; the result has no direct part in evaluating the assay. The difference between the third and the second analyses gives the rise in serum albumin concentration during the week when the test protein was fed. In twenty-three control experiments in which the basal low protein diet was actually fed longer than three weeks, the average decline in albumin during the fourth week was 0.15 gm. per cent. Since the test food should receive credit for preventing this decline, the "assay value" is calculated as the rise in albumin concentration plus 0.15. When assay values are determined for the same food on a number of different animals, the range of biological variation among the results will be fairly wide. It follows that a series of assays must be made before an average value, called "the potency value," can safely be assigned to any one protein.

Table III shows the results of twelve assays of casein by this method. The columns in the table show the albumin levels at the start of each experiment, the levels reached at the end of three weeks of low protein feeding, and the final levels attained after one week when casein was again incorporated in the diet. In the next two columns the loss in concentration during the period of depletion is compared with the subsequent gain. The assay values are obtained by adding the maintenance allowance, 0.15, to the figures which represent gains in grams per cent. The potency value or average of the assay values is 0.388. Although the majority of the assay values are in fairly good agreement with the potency value, I must direct your attention to the extreme variability in

TABLE III

ASSAYS OF *CASEIN* FOR ALBUMIN FORMATION

Dog	*Serum Albumin per 100 cc.*					*ASSAY VALUE*
	Initial	*Depletion*	*Regeneration*	*Loss*	*Gain*	
	gram	*gram*	*gram*	*gram*	*gram*	
B-12	3.81	2.63	2.55	1.18	–.08	0.07
5-7	3.61	2.76	2.79	0.85	0.03	0.18
5-31	4.07	3.04	3.25	1.03	0.21	0.36
7-27	3.40	2.27	2.51	1.13	0.24	0.39
6-35	2.89	1.90	2.14	0.99	0.24	0.39
8-04	3.38	2.52	2.77	0.86	0.25	0.40
9-51	3.46	2.73	2.99	0.73	0.26	0.41
7-28	3.16	2.40	2.70	0.76	0.30	0.45
7-47	3.44	2.47	2.78	0.97	0.31	0.46
3-0	3.80	2.91	3.23	0.89	0.32	0.47
9-49	4.60	3.20	3.54	1.40	0.34	0.49
3-36	3.42	2.66	3.09	0.76	0.43	0.58

POTENCY VALUE: 0.388 ± 0.027 (P.E.)

From the *Bulletin of the Johns Hopkins Hospital.*[11]

TABLE IV

ASSAYS OF *BEEF SERUM* FOR ALBUMIN FORMATION

Dog	*Serum Albumin per 100 cc.*					*ASSAY VALUE*
	Initial	*Depletion*	*Regeneration*	*Loss*	*Gain*	
	gram	*gram*	*gram*	*gram*	*gram*	
1-68*	3.39	2.61	2.80	0.78	0.19	0.42
5-31	4.14	3.23	3.66	0.91	0.43	0.58
3-0	3.69	2.83	3.28	0.86	0.45	0.60
7-31	3.58	2.53	3.02	1.05	0.49	0.64
9-51	3.47	2.59	3.10	0.88	0.51	0.66
2-05*	3.63	2.29	2.71	1.34	0.42	0.74
6-35	3.26	2.42	3.11	0.84	0.69	0.84
9-52	2.61	1.45	2.20	1.16	0.75	0.90
3-36	3.72	2.74	3.63	0.98	0.89	1.04
1-69*	3.02	2.19	2.88	0.83	0.69	1.12
1-55	3.61	2.39	3.51	1.22	1.12	1.27

POTENCY VALUE: 0.801 ± 0.053 (P.E.)

* In these experiments the regeneration period lasted for five instead of seven days. Calculation of the assay values is explained in the original publications. From the *Bulletin of the Johns Hopkins Hospital.*[16]

a few experiments; the extreme cases give a total range among the assay values from 0.07 to 0.58. This tendency for a few animals to diverge widely from average behavior constitutes the major difficulty encountered in experiments of this type. So far we have not learned how to overcome the difficulty except by performing a fairly large number of assays with each food.

Table IV shows the results with the most potent food protein we

TABLE V

	Gelatin	*Casein*	*Beef Liver*	*Beef Chuck*	*Egg White*
Beef Serum (11) 0.801	0.0001	0.0001	0.0003	0.0007	0.042
Egg White (11) 0.613	0.0001	0.0003	0.0026	0.0090	
Beef Chuck (12) 0.475	0.0001	0.098	0.42		
Beef Liver (12) 0.436	0.0001	0.38			
Casein (12) 0.388	0.0001				
Gelatin (4) –.093					

have tested so far, namely, beef serum. Eleven assays have been performed. Only the two lowest assay values overlap with the casein series. The remaining values are higher than any recorded with casein. The potency value for beef serum, 0.801, is more than twice that for casein.

At the present time assays of six foods have been completed. The values for the six foods arranged in order of potency are given in the left-hand column of Table V. Beef serum is first, with a potency value of 0.801. It is significant that Whipple came to the same conclusion by a wholly different method of assay. There follow: egg white (11 assays), 0.613; beef muscle (12 assays), 0.475; beef liver (12 assays), 0.436; casein (12 assays), 0.388; gelatin (4 assays),—0.093. In three of the four assays of gelatin, the albumin level at the end of a week of feeding this protein was less than would have been expected if no protein at all had been fed.

Gelatin therefore appears in the table with a negative value. The remaining columns of the table are given over to a statistical tabulation of the probability that the difference in potency value between any two of the foods is significant. When the tabulated value of the probability integral is less than 0.05, a significant difference may be regarded as established. Beef serum is clearly more potent than casein, beef liver, and beef muscle; the difference between beef serum and egg white is barely significant. Egg white, however, is secure in second place. There is no question concerning the absolute inferiority of gelatin. However, a real difference between beef muscle, beef liver, and casein has not been shown.

The clinical usefulness of assays of this kind remains to be demonstrated. Because physicians have sometimes failed to observe startling distinctions among different food proteins in humans with nephrosis does not mean that qualitative differences such as we have shown to hold for the dog do not also apply in man. The suggestion has already been made that in disease the replenishment of albumin may sometimes be delayed by injury of the organ concerned in synthesis. Such injury when present will complicate greatly the interpretation of dietary experiments on the ward.

* * * * * * * * * * *

In summary: I have traced for you some of the features which characterize the behavior of the albumin fraction of serum, the manner in which it becomes depleted when dietary protein is inadequate and the path of regeneration when adequate feeding is resumed. I have discussed the part in physiology served by albumin by virtue of the osmotic pressure which it exerts, namely, its function in protecting the circulation as blood flows through the capillaries so as to prevent edema and its role in maintaining the volume of the blood. And finally, I have described experiments which look toward the more intelligent management of patients who suffer from depletion of serum albumin.

In conclusion: The material from which this Harvey Lecture was composed was chosen to trace the course of research in a single experimental laboratory. You have honored me in asking that I tell the results of the work, and in turn it becomes my privilege to divide the honor with those who have gone with me: with Dr. Elvira Goettsch who has been my associate for the past seven years; with several technicians who have endured the tedium of thousands of Kjeldahl analyses;

with Boris Gagarin who with devotion has cared for my dogs; and finally with all of those friends and associates at the Medical Center who by conversation and suggestion have been responsible for crystallizing the ideas which have been expressed.

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GENERAL PATHOLOGY OF LYMPHOSARCOMA*

JAMES EWING

WHEN all forms of primary tumors of lymph nodes are combined, the total incidence of this group of diseases becomes quite formidable. A search for statistical data brings to light the notable fact that there are no reliable data on this subject and also that in the present state of knowledge and the attitude of the medical public mind, there is no possibility of obtaining them. The United States Census of 1934 reports 1,512 deaths from pseudoleukemia and Hodgkin's disease, and 3,403 from the leukemias, while the majority of cases of fatal tumors of lymph nodes are classed under cancer of lymph nodes, from which it is impossible to determine how many were primary in the lymphatic system. It is well known that lymphatic diseases are more common in the Orient; and in Batavia, Java, the lymphosarcoma group ranks fourth on the list of deaths from cancer. From this state of affairs, one obtains support for the impression that lymphosarcoma, although a major medical problem, is a badly neglected field of observation, and that until some efforts are made to bring order into this chaos, beginning with nomenclature, little accurate information regarding the economic and social significance of this disease will be available. All that we know is that lymphosarcoma is a relatively common disease, nearly always fatal, of quite obscure etiology and pathology, generally difficult of diagnosis, and little influenced by treatment. All these facts were well known to Paltauf and Kundrat fifty years ago.

Etiological data being largely lacking, we are still compelled to rely upon morphology for the classification of tumors of lymph nodes. Applying this principle, three main structural varieties of these tumors are clearly distinguishable: lymphadenoma, lymphocytoma, and reticulum cell lymphosarcoma. Each of these varieties is associated with rather typical clinical characters and each is doubtless referable to specific etiological factors as yet undetermined. A simple scheme shows how specific structure goes with peculiar clinical course.

* Delivered November 1, 1938, in the Eleventh Annual Graduate Fortnight.

Lymphadenoma:

Multiple giant follicular lymphadenoma–Brill's disease
Gastrointestinal pseudoleukemia

Lymphocytoma:

Systemic pseudoleukemia
Lymphocytic leukemia
Malignant disseminating lymphocytoma
Plasmacytoma
Solitary lymphoma

Reticulum Cell Lymphosarcoma: Large round cell lymphosarcoma affecting many regions and organs

The term lymphadenoma is appropriate because the lymph node is an organ and the lesion reproduces all the features of the organ in more or less orderly fashion but with varying grades of anaplasia and malignancy. In lymphocytoma the cell affected is the lymphocyte, while reticulum cells are passive. All grades of malignancy are observed. It is surprising how tardy has been the recognition of the specific features of reticulum cell lymphosarcoma. The most superficial comparison of the structure of a series of lymphatic tumors reveals the sharp distinctions between the small cell lymphocytic and the large reticulum cell sarcomas.

The early observers including Paltauf did not attempt fine distinctions between the different tumors of lymph nodes, but they fully recognized the two main varieties, small and large cell. Thirty years ago I began to point out to students the histogenesis of the two types of tumors of lymph nodes, and in 1913 in an article on endothelioma of lymph nodes, I discussed this subject in detail, supposing that it was so widely recognized among pathologists as to require little emphasis. Yet it was not until 1932 that an article by Roulet, proposing the term of reticulum cell lymphosarcoma, brought this term into general use. Ringertz of Stockholm has recently reviewed this history in detail.

A sketch of the main features of characteristic cases of the three varieties of lymphatic tumors may serve to emphasize their specific nature.

Lymphadenoma: Multiple giant follicular lymphadenoma is a systemic disease, usually widely generalized when first observed, affecting many or all groups of lymph nodes and the spleen, associated with rather moderate anemia, weakness, occasional mild pyrexia, running a progressive course, favorably affected by radiation, but recurring with increasing severity and generally proving fatal in five to ten years. The tumors

are not large and there is a limited scope of malignancy, but certain cases develop somewhat aggressive tendencies toward the terminal periods. Etiological factors are practically unknown. The structure shows a remarkable predominance and persistence of large, well-formed lymph follicles, with hyperplastic germ centers, with excess of lymphocytes of mainly normal type. In a few cases more diffuse growth may appear and the structure of diffuse lymphosarcoma may be produced.

Gastrointestinal pseudoleukemia is a term designating a very peculiar systemic disease affecting at times the entire gastrointestinal tract; producing myriads of small lymphomas in the mucosa from mouth to anus, without ulceration, and extending to many chains of lymph nodes and spleen; running a steadily progressive and rather active course with some fever, anemia, diarrhea, emaciation, peritonitis, and death within a few years or few months. The structure shows a remarkable tendency to be limited to the growth of many rather well-formed lymph follicles composed of normal or large lymphocytes and few reticulum cells, but lacking the diffuse growth of a malignant tumor or the ordinary type of systemic pseudoleukemia. Etiological factors are entirely unknown. I see nothing gained by merging these specific clinical entities with the general group of lymphosarcoma or pseudoleukemia, while the structural features are accurately indicated by the term lymphadenoma.

Lymphocytoma covers a wide field of clinical conditions and an equally varied morphology, determined mainly by the grade of malignancy and doubtless by the still undetermined etiology of most of its forms. At one end of the series stands the simple solitary lymphoma, a benign tumor composed of a diffuse growth of lymphocytes, occurring in many organs, often reaching a large size, and not recurring after operation or radiation. The average case of systemic chronic pseudoleukemia presents the structure of simple diffuse lymphocytoma. In many such cases a tuberculous etiology is well established. Lymphatic leukemia belongs in this group of lesions. The malignant forms of lymphocytoma present features which distinguish them from other types of lymphosarcoma, particularly from the reticulum cell sarcomas. Billroth's malignant lymphoma was the classic example of the older writers. This disease begins as a localized tumor of one node or chain, rapidly progressing, fusing the nodes, infiltrating the surrounding tissues and producing widespread metastases, generally aggravated by operation, now known to resist control by radiation or prone to recur, and

probably always fatal, with fever, anemia, and cachexia. The pathologist recognizes the terminal stages of malignant lymphocytoma by the widespread metastases, especially in serous membranes and in tissues not normally containing lymphatic tissue, and by the production of many, even myriads, of small lymphomas. The clinician may find little satisfaction in attempting to recognize distinctions between lymphatic disease before which he stands mainly a helpless observer. Intermediate grades of malignancy of lymphocytoma are found among the numerous cases of pseudoleukemia and lymphatic leukemia. That some of the very malignant forms represent terminal stages of the less malignant is illustrated in any broad clinical experience. On the other hand there are obvious differences between the most rapid lymphatic leukemia and the highly malignant lymphocytoma without leukemia. I recall a case of acute febrile lymphatic leukemia lasting eighteen days, with 600,000 leukocytes in the blood and widespread miliary lymphomas in the organs; but the lymphomas failed to affect the serous membranes, were never infiltrative, and exerted only mild pressure effects, whereas in the malignant tumor the lymphomas were universal, destructive, and produced aggressive tumors.

Reticulum Cell Sarcoma covers the main field of the lymphosarcomas and includes the great majority of the cases. The classical description of the older writers deserves repetition. The disease begins in a chain of nodes or in a localized area of a mucous membrane. All the nodes of the chain are affected from the first. The disease spreads by involving other chains of nodes but generally the whole new chain appears enlarged. The method of extension is obscure but probably involves both dissemination of the exciting agent and cell embolism. Isolated bulky metastases appear both in the lymphatic system and in other organs in which the new tumors arise in tissues entirely free from other signs of lymphatic irritation. Yet the primary focus is generally discernible at autopsy and appears to dominate the course of the disease. Hence early excision or radiation of the primary lesion has often controlled the disease. The clinical varieties and manifestations of reticulum cell sarcoma are extremely numerous, affecting every organ and tissue, obtruding themselves into every medical specialty, and at all ages.

Out of this complex clinical field, certain generalizations stand out prominently. There is the very notable healthy robust, overnourished appearance of the average subject of reticulum cell sarcoma, which is

sharply contrasted with most other forms of lymphatic diseases and especially with Hodgkin's disease. There is the tendency to localization, at least temporary, of the primary lesion. There is the tendency to limitation to the organ in which the disease arises, especially noted in lymphosarcoma of skin, spleen and bone marrow. There are rather specific cellular features detectable in lymphosarcoma of spleen, thymus, stomach, and some other organs, on which a localizing diagnosis may often be made. There is a notable frequency for the disease to terminate with streptococcus septicemia. A gloomy generalization relates to the highly lethal prognosis of this lesion in any form, so that one is compelled to regard with gravity the appearance of any spontaneous enlargement of a chain of lymph nodes, especially in an adult.

While the chief structural feature is simple enough, consisting in a diffuse growth of reticulum cells of varying degrees of anaplasia, there is a surprising variety in structural details which render the exact diagnosis and prognosis of lymphosarcoma one of the most difficult tests of the pathologist. It is seldom possible to predict whether the patient will live a few months or several years. Addicts to histological refinements point out certain peculiarities of structure, like Albertoni, who notes the lesser malignancy of tumors in which there are many large clear cells. The experienced pathologist contents himself with recognizing two main classes of structure in large cell lymphosarcoma, one being difficult to separate from a cellular infectious granuloma, while at the other extreme, one places the highly atypical diffusely growing process without any trace of granuloma. A fine intercellular argentophile reticulum is a characteristic structural feature.

In a serious effort to sharpen the diagnostic skill of pathologists, a Registry of Lymphatic Tumors was established at the Army Medical Museum some years ago. It makes progress slowly, chiefly because of the long period of observation required to complete the records, but now contains about 400 cases. It is a valuable mine of observation and opportunity for the student and deserves the hearty support of clinicians and pathologists, but it suffers from the general neglect visited upon the whole subject of lymphosarcoma and is seldom consulted. In this collection, the three classes of lymphatic tumors are fully illustrated and the diagnostic problems sharply emphasized. These problems consist chiefly in the distinctions between simple inflammatory and granulomatous inflammation, between tuberculosis and Hodgkin's disease, the

separation between inflammatory and neoplastic processes, and the recognition of grades of malignancy. All these problems constantly confront the pathologist and they are so difficult that one often wonders whether any adequate classification of lymphatic diseases is possible in the present state of knowledge.

The position of the leukemias in the scheme of lymphatic diseases is not easily determined, and is not adequately covered in the above groups which deal only with true primary tumors. Present knowledge indicates that the leukemic blood picture is a symptom arising under many different conditions and from a wide variety of etiological factors. Some of these processes are purely inflammatory and even transitory, others seem more or less autonomous, irreversible, and neoplastic, while in still others the underlying process is one of the many recognized varieties of malignant tumors of lymph nodes. On the ground that the leukemias are primary diseases of the bone marrow they might be excluded from the class of primary diseases of the lymphatic system. Yet it is unsafe to press this principle too far and for practical reasons the leukemias should be included in the general group of lymphomas. To cover the leukemias and certain other rarer forms of lymphatic disease, it is necessary to expand the classification and add to the three main classes of tumors certain subvarieties. Lymphatic leukemia falls with pseudoleukemia under lymphocytoma. Myelocytic leukemia is a specific process in which granular myelocytes are found in the hyperplastic nodes. Plasma cell leukemia, lymphomas, and lymphadenitis also stand out by themselves.

Endothelioma of lymph nodes: The doctrine that there is a specific group of primary tumors of lymph nodes, derived from the lining endothelium of cavernous and lymph sinuses, producing a structure resembling carcinoma, has been nearly wrecked by the discovery by Regaud and Schmincke of lymphoepithelioma. Probably the great majority of tumors recorded as endothelioma of lymph nodes were derived from the lining epithelium of mucous surfaces in which lymphatic tissue is abundant, as in the nasopharynx. Nevertheless the literature continues to supply rather frequent examples of tumors presenting the rather characteristic structure which the authors derive from lining endothelial cells. In many of these cases a clinical search or postmortem examination, which is stated to be thorough, fails to reveal any primary focus in the mucous membranes. I continue to see occasional cases submitted in which these conditions are asserted to exist and the structure

of the tumor and its clinical course are peculiar. In my own material I have not seen in recent years, any cases of this type in which a primary focus was positively excluded. While unable to deny that a primary endothelioma derived from sinus endothelium exists, I am inclined to think that cases of this type will diminish in frequency as observations become more precise and critical.

Etiology: An attempt to review the clinical data regarding the causation of lymphosarcoma is like looking into a fog at sea, and this impression is aggravated by inspection of current literature. Present day studies are wrestling with morphology, and there is little systematic effort to elucidate the problems of etiology. It is evident that lymphatic hyperplasia and neoplasia may be excited by a great variety of conditions which include every class of external irritant, supported by many contributing factors and favored by certain predisposing causes.

Subacute bacterial infection stands as one of the common excitants of lymphatic tumors, especially of skin and mucous membranes in man and lower animals. The pyogenic cocci, especially the group of streptococci, are most prominent in this relation, but many other microorganisms seem to be concerned in special cases. That subacute streptococcus infection is capable of producing lymphocytic and reticulum cell hyperplasia instead of polynuclear leukocytic exudate, was established long ago. In the skin, staphylococcus, ringworm, and many other common skin infections have been observed to precede lymphomatosis. A careful search for old or recent infections of skin and mucous membranes in cases of lymphosarcoma of these or deeper organs is rewarded with success in a large proportion of such cases and should always be undertaken. It is not an uncommon history that the patient suffered some months or years previously with a local infection accompanied by enlargement of regional nodes which subsided, but after a variable period the lymphatic enlargement returned in the form of lymphosarcoma. In a group of cases of deep lymphosarcoma, there is a history of typhoid fever, appendicitis, cholecystitis, salpingitis, or other local infection for which medical attention was required.

Most prominent among the established causes of lymphosarcoma are the infectious granulomas, including probably all of them, but especially tuberculosis and Hodgkin's disease. Tuberculosis is the chief causative agent in the entire group of lymphocytomas, but its relation to reticulum cell tumors is less definite. The transformation of a hyperplastic tubercu-

lous process into lymphocytoma has been observed many times, and the existence of a tuberculous process in such cases has probably often been overlooked. It has long been known that tuberculous infection with or without many tubercle bacilli may take the form of a nearly pure lymphocytic hyperplasia. In many cases of systemic pseudoleukemia, definite foci of tuberculosis may be found at autopsy.

The scope of morphology of Hodgkin's granuloma is so wide and its causative agent so uncertain that no definite statement may be made regarding its relation to lymphosarcoma. Hodgkin's granuloma affects reticulum cells more than lymphocytes, and one may assume that any lymphosarcomatous process arising on the basis of Hodgkin's disease would take the form of reticulum cell sarcoma. In typical cases of Hodgkin's disease, sarcomatous features may develop, involving the reticulum cells, but the process does not greatly resemble the typical reticulum cell sarcoma. That Hodgkin's disease ever takes the form of a true malignant neoplasm has never been proven, but it may be that certain cases of reticulum cell sarcoma arise on the basis of a Hodgkin's infection. Hodgkin's is the most typical of all the infectious granulomas, and the rather popular theory of its essential neoplastic character is without foundation.

An important relation of syphilis to any of the primary tumors of lymph nodes is not supported by very substantial data. Several less common infectious granulomas should probably receive more attention as possible causes of lymphomas. Micrococcus melitensis and venereal lymphogranuloma produce lesions closely resembling some of the atypical lymphomas, and subinfections by these agents may be concerned with some of the lymphosarcomas.

In the gastrointestinal tract, granulomas of undetermined origin affect stomach, bowel, appendix, and rectum, and produce lesions which greatly resemble in most respects the fully developed lymphosarcomas of these regions. Through such portals of entry, the deep thoracic and abdominal nodes are probably infected. In all cases of retroperitoneal lymphosarcoma, the gastrointestinal tract should be carefully searched for healed or small active lesions.

Constitutional factors seem to play a prominent part in the causation of the typical cases of reticulum cell sarcoma. This disease is remarkable for its predilection for robust, over-nourished, florid types of individuals who maintain their euphoria nearly to the terminal periods. Most of the

cases of Brill's disease also occur in such subjects. Veterinarians are quite familiar with the frequency of lymphosarcoma in cattle bred for the market, for hundreds of such animals are condemned every year for lymphomatosis. The nature of the predisposition established in such subjects is at present wholly obscure.

Experimental cancer research has brought out some peculiar etiological factors, the relation of which to human disease is quite uncertain. In mice, leukemia is produced by innoculation of cells and some strains are susceptible, others refractory. Leukemia has been produced experimentally in fowl by cell free extracts (Furth), by extracts of normal organs (Schridde), by benzol (Bungeler), and by radiation by radium or x-rays. Occasionally, leukemic or lymphomatous processes arise after the application of the cancerigenic cyclic compounds.

Criteria of Lymphatic Tumors: In the interpretation of lymphatic tumors, certain special criteria must be considered. Lymphatic tissue is present in nearly all tissues of the body and the total amount of this tissue is quite large. Lymph nodes are not fixed organs but come and go, varying in different species of animals, at different ages, in individuals, and in response to changing physiological conditions. The lymph node is the first barrier against infection which has passed the skin or mucous membrane, and the lymphocyte responds to irritation more readily than any other cell except the polynuclear leukocyte. The scope of reversible inflammatory hyperplasia is very wide and the existence of an irreversible neoplastic hyperplasia should not be assumed unless the autonomous characters are pronounced. There are physiological distinctions between systemic, thymic, and splenic cells and these often are traceable in tumors of these organs. There are free connections within the lymphatic system and with the blood vessels which render lymphatic tissue more or less mobile. This relation probably accounts for the tendency of lymphatic diseases to become systemic. It renders difficult the interpretation of metastases. There are indications that the extension of lymphatic tumors proceeds chiefly by cell embolism, but often by the development of new tumor cells by diffusion of the exciting agent. The possibility exists that growth stimulating cell products diffusing from the primary tumor focus may play a part in the remarkably wide and rapid extension of some lymphatic tumors. At times the whole lymphatic system seems to react as a whole.

There is a remarkable relation between lymphocyte and reticulum

cell most obvious in the follicles. Flemming's theory that the reticulum cells of the germ center are the mother cells of lymphocytes has been abandoned, for embryological and pathological data point strongly to the view that these two types of cells are distinct. In most pathological processes this distinction is rigidly maintained, but it cannot be denied that in some pathological conditions the two types of cells seem to grow together and the usual sharp distinctions are obliterated. The lymphocyte may reach considerable dimensions, while in some very active reticulum cell sarcomas, the cells may be rather small. Yet I have never seen any definite evidence of the existence of a mixed lymphocytic and reticulum cell sarcoma. The reticulum of reticulum cell sarcoma is usually prominent in this process while regularly absent in all stages of lymphocytoma. The growth of reticulum may account for the tendency to fibrosis observed in many reticulum cell tumors. Necrosis is notably lacking in both classes of lymphatic tumors. The failure of the lymphocyte to provide immunity against the infecting agent is a remarkable feature lacking explanation. This failure may be held responsible for the lethal character, however delayed it may be, of most lymphatic tumors and its granulomas. When enlarged lymph nodes appear anywhere in a subject after puberty, the outlook is always serious.

For many years pathologists have expressed the feeling that lymphosarcomas are not true tumors but require separate positions among pathological processes. They find that this process is so intimately connected with and dependent upon infection or extrinsic irritation, and presents so many features of an inflammatory process, that it may not be given a definite place among strictly autonomous neoplasms. This fact should be noted by workers with various so-called tumors among lower animals.

The foregoing sketch of the problems of lymphosarcoma impresses the critical observer mainly with the fragmentary character of our knowledge of this group of diseases. Every pathologist will admit that when faced with the simple question of diagnosis, he has as a rule to be content with a vague report on the general morphology of the process, but can offer little help regarding etiology, and must rely for prognosis on the generally fatal tendency of the disease. Regarding essential factors controlling the origin and progress of the disease, he must confess nearly complete ignorance. The clinician records the various incidents marking the course of the disease, but must acknowledge his inability

to alter the course except temporarily in the great majority of cases. His inquiry into etiological questions is handicapped by the absence of definite leads from the pathological side. The therapeutics of lymphosarcoma, although considerably encouraged by the occasional recoveries after radiation, is a gloomy chapter. The comparative frequency of these lymphatic diseases, and their occurrence in apparently healthy subjects of all ages, most of whom die in spite of all efforts, discourages optimistic attempts to improve the situation by clinical resources. Recognition of these outstanding facts has led to the establishment of at least one Foundation directed to the systematic study of one group of cases, the leukemias, while tragedies in many families have occasionally led to the granting of small sums to support of isolated workers. While the leukemias have been systematically pursued by experimental workers in several localities under the Tata Foundation, most of the work is undertaken by individuals who take up phases of the subject, pursue them for a time, and then become discouraged by the paucity of results, abandon the study, and wait for others to take up the burden and begin all over again.

Any comprehensive estimate of the scope of the problems of lymphosarcoma must lead to the conclusion that unless there is a systematic attack over a long period by a group of competent workers, under favorable conditions, with adequate material support, and including all phases of the subject, it is unreasonable to hope for any great progress. With this conviction in mind, the writer ventures to outline a program of systematic investigation which might be expected to bring some light on the fundamental questions involved, and possibly lead to some progress toward the prevention and control of this group of diseases. In offering the plan, it is realized that syndicated research has seldom been very successful in solving the major problems of medicine and that there are many practical difficulties in carrying out any such prolonged program even under the best auspices.

Plan of Systematic Investigation of Lymphosarcoma

Clinical medicine: The clinician may investigate the importance of heredity, the relation to status lymphaticus, and the possible relation of the endocrine organs. Metabolic studies are indicated as affecting the soil for bacterial growth. The history of the main organ affected should be searched for. The usual clinical data should be analyzed statistically.

The epidemiology of the disease should be considered.

Pathological anatomy: Full autopsies and study of all organs should be obtained. Chronic lesions in the affected organs should be noted, especially the oropharynx and gastrointestinal tract. The pathology of metastases should be more carefully investigated and interpreted. Radiographs of injected tissues might give important data. The relation between structure and prognosis should be determined in a large series.

Bacteriology: Bacterial studies of surgical and postmortem material should be pursued by appropriate methods. Little is known about the serology or immunology of the disease. The relation to bacterial antigens, and the effects of antigens made against whole tissues and tissue extracts and isolated bacteria invites attention. Bacterial mutation in the presence of lymphatic tissue is to be considered.

Experimental pathology: The reactions of lymphatic tissue to all the common pyogenic bacteria, infectious granulomas, and many chemical agents should be systematically determined. The reactions of lymph nodes to various tissue extracts, lipoids, and proteins of the tumors should be studied. The element of hypersensitization of lymphatic tissue may be considered. The action of known cancerigenic chemicals should be determined in lymph nodes. Do specific agents act selectively upon lymphocytes and reticulum cells?

Therapeutics: Radiological treatment should be standardized, and new modalities should be employed. The use of arsenicals in various combinations and as adjuvants to radiation is suggested by the work of Dustin. Antibacterial agents should be sought to control complications and terminal infections. The position of surgery should be determined.

Diagnosis: The standard of general diagnosis should be improved by the collection of a large series of fully observed cases as in the Lymphatic Tumor Registry. There might well be established a central bureau where very experienced observers would furnish diagnosis and prognosis. The general literature of the entire subject should be made available.

Such a project should be located in an institution or center where material is abundant, and where all the necessary scientific and clinical aids would be available or constantly occupied with one or more of the main problems. If such an organization were established, it would at least provide a center of reliable information and guidance, which is now lacking, and it would soon reveal the futility of the present efforts directed toward the solution of one of the major problems of medicine.

PRESENT STATUS OF SERUM THERAPY IN PNEUMONIA*

RUSSELL L. CECIL

IT IS interesting to compare the development of serum therapy for pneumonia with that of some other forms of specific therapy, such as diphtheria antitoxin for the treatment of diphtheria or insulin for the control of diabetes. In the two latter conditions the specific agents were produced in almost perfect form from the very beginning. Because of this perfection, the medical profession took hold of the new agents with much alacrity and enthusiasm and within a year after their introduction, diphtheria antitoxin and insulin were being widely used by physicians.

The serum therapy of pneumonia, on the other hand, has had a gradual evolution. There have been many obstacles to be overcome and considerable skepticism and indifference on the part of the medical profession to be combatted. The original Type I serum as produced by Cole[1] and his associates was applicable for only Type I pneumonia and, furthermore, the patient's sputum had to be typed by a laborious and time-consuming method before the serum could be administered.

The original Type I serum was bulky and had to be given in large quantities to be effective. As a result, inadequate amounts were often administered, and disappointing results were obtained. The large amount of horse protein in the serum caused severe serum sickness in many patients and the danger of anaphylactic shock and thermal reactions enhanced the unpopularity of the product. In spite of these drawbacks, however, the original Type I serum of Cole was an effective therapeutic agent. Its value was proven by the clinical and statistical evidence submitted by Cole and his co-workers,[1] and by the experimental studies of Cecil and Blake[2] on monkeys.

It has been just twenty-five years since the publication of the first articles on the use of Type I serum at the Hospital of the Rockefeller

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Institute.[1] It is therefore a fitting time to review briefly the advances which have been made in the serum therapy of pneumonia during the last quarter of a century.

First came the studies of Gay and Chickering,[3] Huntoon,[4] and finally the important investigations of Felton,[5] all of which showed that the specific antibodies in antipneumococcus serum could be separated by various chemical or biological procedures from the greater part of the protein content of the original serum. Felton[6] went still further and succeeded in concentrating antibodies until the refined and concentrated product contained five or ten times as much antibody per unit of volume as the original serum. The achievements of Felton simplified greatly the administration of serum and reduced considerably the incidence and severity of reactions.

This improvement in antipneumococcus serum was followed by extensive statistical studies by Cecil and his co-workers[7] at Bellevue Hospital, by Bullowa[8] at Harlem Hospital, and by Heffron,[9] and Sutliff and Finland[10] at the Boston City Hospital. The results obtained in these studies in city hospitals were not only impressive clinically but afforded convincing statistical evidence of the value of pneumococcus serum in Type I pneumonia. By using the alternate case method, it was shown that the death rate could be cut more than half by the use of serum. When only early cases were included, the fatality rate was reduced from the standard 30 per cent to less than 10 per cent.

The next important step in the development of antipneumococcus serum was the complete classification of pneumococci by Georgia Cooper and her co-workers.[11] A Type II antipneumococcus serum had already been tried with promising results, but with the demonstration of thirty odd types of pneumococci, the whole field of serum therapy in pneumonia was greatly widened.

It was fortunate that about this time Neufeld's[12] Quellung reaction was rediscovered and this led to a greatly simplified and accelerated method of typing pneumococci from the sputum and other body fluids. Whereas heretofore it had been necessary to inject a mouse with the sputum and then wait eight to twenty-four hours before testing the exudate, it was now possible by the Neufeld method to determine the type directly from fresh sputum within an hour or two after the sputum had been sent to the laboratory. This contribution has had a most important influence on the serum therapy of pneumonia, for even with

thirty odd specific antisera ready for administration to the pneumonia patient, much valuable time would be lost if we still had to determine the type by putting every sputum through the peritoneum of a white mouse.

One of the most recent advances in the specific therapy of pneumonia has been the introduction of antipneumococcal rabbit serum. This work also emanates from the Rockefeller Institute, and the first report in 1937 by Horsfall, Goodner and MacLeod,[13] created wide attention and interest.

At the present time both horse serum and rabbit serum are available for the treatment of pneumonia. It will probably take several years of comparative study and investigation before we can be sure which serum has the greater merit. Some workers believe that rabbit serum is distinctly preferable to horse serum; others believe that so long as the serum is highly potent, it makes little difference from what animal it is derived.

No serum should be used unless its potency is known. The strength of serum is measured in units "per cc.," the unit being that amount of antibody which will protect a white mouse against one million fatal doses of virulent homologous pneumococcus culture.

Antipneumococcus serum is usually dispensed in vials containing ten to twenty thousand units. Cloudy serum should not be used. At the present time in the City of New York, the Department of Health provides antipneumococcal horse serum for Types I, II, V, VII and VIII. Some of the biological manufacturers, however, are going further, and provide antipneumococcal rabbit serum for the less prevalent types, such as Types III, IV, VI, XIII, XIV, XVII and XIX.

I believe that every case of pneumonia from which a definite pneumococcus type is determined and for which there is an available serum, should have serum therapy. Even apparently mild infections should usually receive serum, not only because it shortens the disease, but because an apparently mild pneumonia may suddenly become a very severe pneumonia. The only contraindications to serum therapy are terminal pneumonias and marked allergic states. With two types of serum available, it will often be possible to circumvent an allergic condition by giving a serum to which the patient is not sensitive. In patients with very low blood pressure, intravenous injections of glucose and saline may be given before starting the serum. In any case, the physician should have a good reason for withholding serum, for he assumes considerable re-

sponsibility in so doing.

The use of antipneumococcal serum in the pneumonias of infants and children appears to be justifiable in many cases. I have had comparatively little experience with infantile pneumonia. However, C. H. Smith[14] at Bellevue Hospital and Bullowa[8] at Harlem Hospital have both reported excellent results with serum therapy in the types of pneumonia which are most frequently encountered in childhood, namely Types I, VI, XIV and XIX. In children the serum may be given intramuscularly or intravenously.

Tests for Sensitivity

No patient should be given antipneumococcus serum without careful inquiry as to the incidence of hay fever, asthma and urticaria. Patients should also be questioned concerning previous injections of serum. Asthma is not necessarily a contraindication to serum therapy, provided there is no sensitivity to the serum that is to be employed; but in administering serum to an asthmatic, the physician should proceed with great caution.

Intradermal Test. Once a decision has been reached to administer serum, the preliminary intradermal and conjunctival tests should be performed. For the intradermal test, two injections are made on the forearm at least two inches apart. The first contains a drop of 1:10 dilution of normal horse serum. The other, a small drop of physiological salt solution, serves as a control. In a positive reaction the wheal becomes larger and is surrounded by a zone of erythema. In a strongly positive reaction, pseudopodia are present. The conjunctival test is performed by inserting a drop or two of 1:10 dilution of normal horse serum in the conjunctival sac of one eye. In case of a positive reaction, the conjunctiva becomes injected and there is itching and watering of the eye. The readings for both tests should not be made for fifteen minutes after the injection of the serum. Antipneumococcus serum may be administered with caution in the presence of a weakly positive skin test. In the presence of a positive eye test, serum should be withheld.

Desensitization. In a highly sensitive patient, desensitization is almost impossible to achieve and should not be attempted without consultation. The writer can recall two cases in which it was tried with very nearly disastrous results. A temporarily refractory state may be produced by means of adrenalin, during which adequate doses of serum may often

be given. An injection of 0.5 to 1.0 cc. of adrenalin five to ten minutes before the serum is administered usually suffices. Small doses of well-diluted serum are given first in gradually increasing amounts before attempting the full therapeutic dose.

Occasionally during the administration of serum, a crop of urticarial wheals appear, with intense itching. In such a case, the serum should be promptly discontinued and adrenalin given subcutaneously. After a short while, the remaining dose of serum may be administered.

A somewhat different procedure has been recommended before administering rabbit serum. A preliminary intravenous test is made by injecting 0.1 cc. of the type-specific rabbit serum, diluted with 0.9 cc. of saline solution. The pulse and blood-pressure are taken before the injection and five minutes following it. It is claimed that if a patient is sensitive to rabbit serum, there will be a fall in the arterial blood-pressure of twenty or more mm. of mercury and an increase in the pulse rate of twenty or more beats per minute. In the presence of such a reaction, rabbit serum should not be administered.

Administration of Serum

If the sensitivity tests are negative, we proceed at once to the administration of serum. A syringe containing 1.0 cc. of adrenalin should first be prepared to meet any emergency that might develop during the injection of the serum.

It is customary to give a small intravenous injection of serum before giving the full therapeutic dose. The amount injected differs in different clinics; usually 1.0 cc. of serum, diluted with 9.0 cc. of saline is administered very slowly with constant attention to the color and pulse rate of the patient. Such a small dose of course has no therapeutic value but if the patient takes it without any reaction, the physician will have a good deal more confidence in giving the full dose. If after one hour there is no reaction to the preliminary injection, we proceed to give 10 to 20 cc. of serum intravenously depending on the potency of the agent. With the present concentration of serum it is possible to give the average complete dose of one hundred thousand units in three to four injections of serum. In bacteriemic cases, two hundred thousand units should be administered during the first twelve hours of treatment. On the morning after the injection of serum, patients who have been treated early usually show a striking improvement. The temperature and pulse rate will have

dropped to normal or almost normal and the whole appearance of the patient will have changed for the better. In cases in which marked improvement has not taken place within twenty-four hours after the injection of serum, the question will naturally be raised as to the accuracy of the typing. Unfortunately errors in typing are fairly common, though it must be added in defense of the bacteriologist that these mistakes often occur through no fault of technique. The first specimen of sputum may not contain the infecting type of pneumococcus at all; or it may yield two types of pneumococci, thus leaving the physician somewhat confused as to which type of serum to administer. Even in some correctly typed cases, however, little if any improvement will be noticed on the second day and it may be necessary to give more serum. This is particularly true in patients over forty-five years of age and in those with more than one lobe affected. It is also observed in cases where serum is started after the third day. In any case, serum should be continued until the temperature and pulse rate return to normal or until the intradermal or agglutination tests are definitely positive. The intradermal test and the agglutination tests are somewhat difficult to carry out unless the patient is in a hospital; and in the last analysis, neither is so dependable as the clinical condition of the patient.

An excellent rule to follow is to take a blood culture on every patient with pneumonia just before the administration of serum. The presence or absence of bacteriemia is of the greatest import so far as prognosis is concerned, and furthermore the dosage of serum is doubled in the presence of sepsis.

It is well to remember that when a lapse of several days has occurred since the administration of serum, the greatest caution must be observed if serum therapy is to be renewed. Otherwise a fatal anaphylaxis may occur.

In some clinics there is a tendency now to give the entire therapeutic dose of serum in one injection. This procedure has come into vogue since the introduction of rabbit serum. However, for the general practitioner, particularly in treating a patient in the home, it is a safer practice to divide the serum into several doses. There is also a tendency to give a larger dosage when using rabbit serum. Horsfall and his colleagues[18] at the Rockefeller Institute often give 250 thousand units of antibody with one injection of serum.

Serum Reactions

The various reactions to serum therapy are now familiar to most physicians. In the acute allergic reactions which appear during or shortly after administration, the patient becomes dyspneic, flushed and cyanotic; the pulse is rapid and weak and there is apprehension, tightness in the chest, and often a desire to urinate or defecate; in some cases there is also nausea and vomiting. In the occasional fatal reactions, the pulse becomes imperceptible and there is marked cyanosis followed by respiratory failure and death. Acute allergic reactions are promptly relieved by injections of 0.5 to 1.0 cc. of adrenalin administered subcutaneously and well rubbed in. It is not necessary to inject the adrenalin directly into the vein. Thermal reactions are not so common now as they were in the early days of serum therapy. Occasionally, however, the patient will have a chill an hour or so after the injection of the serum, followed by a rise of one to four degrees in temperature. Usually there is a rapid drop, followed by profuse perspiration, but occasionally the temperature remains high (107° to 108° F.) and the patient may go into a profound shock and stupor. In case of hyperpyrexia, cold packs and ice water enemas should be used together with emergency stimulation. Serum sickness is another form of serum reaction which is much less frequently seen now than formerly. The giant urticaria which so often followed serum in the early days is now a rare complication. Mild urticaria develops in 15 to 20 per cent of patients who receive the modern concentrated and refined forms of antipneumococcus serum.

Results of Treatment

The introduction of antipneumococcus serum has revolutionized the treatment of pneumonia. The use of serum not only reduces the fatality rate by more than one-half but, if given early, prevents bacteriemia and greatly shortens the duration of the disease. The results of serum therapy for the various types are shown in Table I.

These figures have been compiled from the statistics of a number of different observers. The largest series is naturally the Type I group, for which serum has been used for many years. The death rate is cut from 32.6 per cent for controls to 13.6 per cent for serum treated cases. The results of serum treatment in Type I pneumonia have been remarkably consistent. For example, Lord and Heffron[15] report 1043 cases of

TABLE I

FATALITY RATES FOR PNEUMOCOCCUS PNEUMONIA OF THE COMMONER TYPES, WITH AND WITHOUT SERUM*
(HORSE SERUM ONLY)

Type of Pneumococcus	*Serum Treated*			*No Serum*		
	No. of Cases	*Deaths*	*Mortality Per Cent*	*No. of Cases*	*Deaths*	*Mortality Per Cent*
I	3136	429	13.6	558	182	32.6
II	964	302	31.3	967	424	43.8
V	139	35	25.1	516	187	36.2
VII	109	13	11.9	404	117	28.9
VIII	41	4	9.8	319	60	18.8
XIV	39	4	10.2	167	34	20.3
TOTAL	4428	787	17.7	2931	1004	34.2

TABLE II

FATALITY RATES FOR PNEUMOCOCCUS TYPES I & II TREATED WITHIN AND AFTER SEVENTY-TWO HOURS

Pneumococcus	*Cases Treated Within 72 hours of onset*			*Cases Treated 72 hours, or more, after onset*		
	No. Cases	*Deaths*	*Mortality Per Cent*	*No. Cases*	*Deaths*	*Mortality Per Cent*
Type I	844	79	9.3	979	170	17.3
II	62	10	16.1	40	16	40.0

TABLE III

RESULTS OF SERUM THERAPY IN BACTERIEMIC CASES OF PNEUMONIA

Pneumococcus	*Serum Treated*			*No Serum*		
	No. Cases	*Deaths*	*Mortality Per Cent*	*No. Cases*	*Deaths*	*Mortality Per Cent*
Type I	651	225	34.5	325	225	69.6
II	189	105	55.5	381	282	74.0
V	36	26	72.2	113	87	76.9
VII	13	2	15.4	71	61	85.9
VIII	15	5	33.3	126	57	45.2
TOTAL	904	363	42.2	1016	712	70.0

* The figures presented in Tables I, II and III have been compiled from the published statistics of various writers.

Type I pneumonia treated with serum with a death-rate of 13.9 per cent. Rogers[16] reports that in 1023 cases of Type I pneumonia, treated with serum during the first four days of the disease, the death rate was also 13.9 per cent! Even lower figures have been obtained by Cole[17] at the Rockefeller Institute and by Bullowa[8] at the Harlem Hospital. Cecil and Plummer[7] obtained a higher figure at Bellevue, where 410 Type I pneumonias that received specific therapy had a death rate of 17.6 per cent.

In Table I it will be noted that the fatality rates for the other prevalent types of pneumonia are also very favorably affected by serum therapy. The total for 4428 cases of pneumococcal pneumonia treated with specific serum yields a fatality rate of 17.7 per cent, compared with 34.2 per cent for 2931 cases that received no serum.

Both Type II and Type III pneumonia have offered considerable resistance to serum therapy, presumably because they are both severe forms of pneumonia and have a natural fatality rate of 40 to 50 per cent. Thanks to more potent serum, Type II is now being favorably affected by specific therapy, but Type II pneumonia should be very promptly treated and with large doses of serum. In Table II, we show the importance of administering serum early in the disease.

The fatality rates of serum-treated cases are distinctly lower for those patients treated within the first seventy-two hours than for patients treated seventy-two hours, or more, after the onset of the disease.

In bacteriemic cases, the death rates for all types of pneumococcal pneumonia are double or triple the usual figure but here again the value of serum therapy is well shown. In Table III, the results of serum in bacteriemic cases are shown for the five prevalent types.

The fatality rate for septic cases treated with serum is 42.2 per cent, compared with 70 per cent for the septic cases that received no serum.

Type III Pneumonia. Pneumococcus Type III pneumonia still presents a serious therapeutic problem and because of the disappointing results obtained with serum therapy, efforts have been made to control the disease by chemotherapy, or by a combination of serum therapy with chemotherapy. For example, Rosenthal,[18] Long and Bliss,[19] and Cooper, Gross and Mellon[20] have reported favorable results with sulfanilamide in white mice and rats infected with pneumococcus Type III.

Heintzelman[21] has recently reported a series of nine cases of pneumococcus Type III pneumonia treated with sulfanilamide, with a fatality rate of only 22 per cent. The series is too small, however, to be of

much significance. In the very interesting bone marrow studies of Osgood,[22] the author showed that Type I antipneumococcal serum was more effective against Type I pneumococcus than sulfanilamide. However, he then showed that sulfanilamide plus a given dose of antiserum was more effective than corresponding doses of antiserum alone. His results support the view that sulfanilamide renders the pneumococcus more vulnerable to bactericidal substances present in the serum. In view of these findings, it would seem that further observations on the combined effect of sulfanilamide and type-specific antipneumococcal serum are in order.

Because of the favorable results obtained with sulfanilamide in frank Streptococcus hemolyticus infections, it is natural that chemists should be striving to obtain some derivative of sulfanilamide which will exercise a similar specific effect on pneumococcal infections. Up to date, the most promising synthetic agent of this kind is that advocated by Whitby,[23] who observed that 2-(p-aminobenzene-sulphonamido) pyridine protects mice effectively against 10,000 lethal doses of Types I, VII and VIII. This drug is frequently referred to as Dagenan or M. & B. 693. Fleming,[24] working with the drug *in vitro*, noted that its effect was bacteriostatic rather than bactericidal. He found no deleterious effect from the drug on the leukocytes and further noted that the efficiency of the agent was enhanced in the presence of specific immune serum. He suggested that to obtain the best results, the patient should be given specific serum as well as M. & B. 693. The drug appears to be less toxic than sulfanilamide though, if kept up for any time, it frequently causes nausea and vomiting. Evans and Gaisford[25] have recently reported in the *Lancet*, 100 cases of pneumococcus pneumonia treated with M. & B. 693. A control series of 100 cases was observed at the same time. A fatality rate of only 8 per cent was observed in the treated cases, while that for the untreated cases was 27 per cent. The weakness in this report is that quite a large proportion of the cases treated were not typed. At the present time Dagenan (M-B 693) is being tried out clinically in a number of New York hospitals. In many cases the results have been quite striking but in certain other cases, especially those treated late, the drug has not prevented a fatal termination. Perhaps the ideal combination may eventually prove to be a combination of specific serum with chemotherapy. Under any circumstances Dagenan must be looked upon as an important and promising addition to our pneumonia therapy, though

obviously still in the experimental stage.

The writer wishes to say a final word about the treatment of pneumonia in private practice. In a recent study with E. A. Lawrence,[26] we analyzed 911 cases of pneumonia from the records of private practice with especial reference to the incidence and fatality rates for different types and the results of serum therapy. The data obtained from the private practice series were compared with well-established data based on records from the public wards of large city hospitals. The most significant facts brought out by this study were:

1. The generally higher age incidence of pneumonia in the well-to-do classes.

2. The high incidence of pneumococcus Type III pneumonia in private practice. This probably resulted from the higher age incidence of this group.

3. Inadequate bacteriological study of private cases. Less than half of the patients available for the study had been properly typed.

4. Only 60 per cent of the private pavilion patients with Type I pneumonia received Type I serum. In the consultation series, a higher proportion received serum but the results of serum therapy in both series were not so favorable as those obtained in the wards of large city hospitals. The fatality rate of 23.5 per cent for the entire series of 115 private cases of Type I pneumonia in which serum therapy was given is almost double that reported from various other sources and is not conspicuously lower than the standard fatality rate for Type I non-serum treated cases. A number of factors such as the higher age incidence, delay in administering serum, and inadequate dosage of serum are presumably responsible for this high figure. Pneumonia in private practice is not so mild as it has often been considered. In view of the proven value of serum therapy in pneumonia, the administration of serum should be part of the routine treatment in every case amenable to serum therapy, regardless of the social status of the patient.

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TREATMENT OF PNEUMONIA WITH ANTIPNEUMOCOCCAL RABBIT SERUM*

COLIN M. MACLEOD

STUDIES of the differences in the physical, chemical, and immunological properties of horse and rabbit antipneumococcal serum led to the conclusion that rabbit serum might have certain advantages over horse serum as a therapeutic agent in pneumococcal pneumonia.

Certain of these differences have been known for a number of years. In 1923 Zinsser and Parker[1] observed that *in vitro* complement fixation does not occur when the specific pneumococcal polysaccharides are mixed with immune horse serum, whereas it does take place in mixtures of these polysaccharides and immune rabbit serum.

Avery and Tillett[2] demonstrated that the injection of horse antipneumococcal serum does not passively sensitize guinea pigs to subsequent injection of the specific pneumococcal polysaccharides, while with immune rabbit serum the guinea pig can be passively sensitized.

Similarly, it was found by Heidelberger and Goebel[3] that horse and rabbit antipneumococcal serum differ in their precipitin reactions when mixed with the partially hydrolyzed specific polysaccharide. This was further investigated by Heidelberger and Kendall.[4]

Goodner[5] noted that rabbit antipneumococcal serum was more effective than horse antiserum in the treatment of rabbits infected by the intradermal injection of virulent pneumococci.

The introduction in 1929 of the quantitative precipitin method by Heidelberger and Kendall[6] opened the way to the more exact study of the immunological behavior of antipneumococcal sera. It was shown by Heidelberger, Sia, and Kendall[7] that the antibody content of horse antipneumococcal serum as measured by mouse protection tests, paralleled fairly closely the amount of specifically precipitable nitrogen in such serum. This was also found to be true of rabbit serum by Heidelberger and Kendall.[8]

* From the Hospital of The Rockefeller Institute for Medical Research.
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By comparing the amount of specifically precipitable nitrogen with the mouse protective potency of both horse and rabbit serum, Goodner and Horsfall[9] demonstrated that each milligram of specifically precipitable nitrogen in rabbit serum corresponds to approximately 1200 mouse protective units, whereas with horse serum the same amount of specifically precipitable nitrogen represents between 500 and 800 mouse protective units. The use of the quantitative precipitin method, and the extension of this principle by Heidelberger and Kabat[10] to the quantitative determination of agglutinin nitrogen has been of great value in the standardization of rabbit antipneumococcal serum and will be discussed briefly later.

Goodner, Horsfall and Bauer,[11] by the technique of ultrafiltration through graded collodion membranes, determined that the antibody protein molecule of immune rabbit serum is much smaller in size than that of horse serum. Heidelberger, Pedersen and Tiselius[12] reached the same conclusion using the technique of ultracentrifugation. These observations explain in part the difference in the amount of protein nitrogen precipitated from immune horse and rabbit serum by the specific pneumococcal polysaccharides.

In experimental pneumococcal infections in the mouse the amount of immune horse serum which must be used to overcome the infection has been found to lie within certain limits. If an excess of horse serum is given, the protective action may disappear entirely. This "prozone" phenomenon was not observed by Goodner and Horsfall[13] in the case of immune rabbit serum.

In mouse protection experiments, the same investigators[14] noted that small amounts of cholesterol or cephalin block the protective action of horse antipneumococcal serum, but are without effect in the case of rabbit serum. Although the significance of these observations as applied to pneumococcal infections in man is unknown, they are nevertheless of great theoretical interest.

Certain practical considerations were emphasized by Horsfall, Goodner and MacLeod,[15] in suggesting the use of rabbit antipneumococcal serum in the treatment of pneumonia. Up to the present time it has been relatively difficult to produce in the horse, serum of high titer against pneumococci of certain types. This has been particularly true of Type II serum. On the other hand, in the rabbit, provided certain precautions are observed in the preparation of the suspensions of pneumococci to be

used for immunization,[16] serum of high potency can be prepared against pneumococci of practically all types. Even in the case of Type III pneumococcus, antiserum of moderately high titer has been obtained fairly regularly in the rabbit, whereas serum of high titer can be produced in the horse only irregularly and with great difficulty. The relative ease of immunizing rabbits with pneumococci of the various types has been one of the strongest arguments in favor of using this serum and has led to its present widespread employment against pneumococcal infections of many types. It is of interest that in the rabbit within a period of from four to six weeks, Type I antipneumococcal serum can be prepared, which in its unconcentrated form has frequently the same potency as the concentrated Type I horse serum in current use.

The standardization of antipneumococcal serum has always presented certain difficulties. The method currently used is that of mouse protection employing a standard serum as a reference. In this technique, unless very large numbers of mice are used, the accurate standardization of serum is impossible. The estimation of the amount of specifically precipitable nitrogen in rabbit serum, however, provides a more precise method, since the ratio between specifically precipitable nitrogen and mouse protective units is practically constant in rabbit serum under given experimental conditions. This method has not been applicable to the standardization of horse serum, since it appears to contain antibody fractions of differing avidity for the specific pneumococcal polysaccharide, and these fractions show wide differences in their mouse protective capacity.[9] Consideration of these and other differences in the behavior of horse and rabbit antipneumococcal serum led to the clinical trial of rabbit serum in the treatment of pneumonia.

The same procedures which have been widely employed for the testing of patients for sensitivity to horse serum are applicable to sensitivity tests with rabbit serum as well. Most important of all is an accurate history with reference to allergy, and previous parenteral administration of foreign protein.

Individuals who have acquired sensitivity as a result of previous injections of horse serum, are not ordinarily sensitive to rabbit serum. However, it must be borne in mind that patients with a history of allergy, for example, those who suffer from allergic asthma and are known to be sensitive to horse serum, are also likely to be sensitive to rabbit serum.

In order to determine sensitivity to rabbit serum, intradermal and intraconjunctival tests are made with normal rabbit serum diluted 1:100 with salt solution, precisely as with horse serum. The dilution of 1:100 is important, since when normal rabbit serum is used intradermally in a dilution of 1:10, the skin of many patients will show a non-specific flare reaction. This may be difficult to distinguish from the true allergic reaction which consists of a wheal with surrounding erythema.

The intravenous injection of a small amount of serum is not to be recommended without first knowing the results of the skin and eye tests, since anaphylactic shock may occasionally occur in extremely hypersensitive individuals following the intravenous injection of as little as 0.1 cc. of well diluted serum. As a further precaution after the results of the skin and eye tests are known, it has been our practice to inject slowly intravenously 0.1 cc. of the therapeutic serum diluted to 5.0 cc. with normal saline. If a fall in blood pressure and an elevation of the pulse rate do not occur, it is considered safe to proceed with the therapeutic dose of serum.

The reactions which may occur following the intravenous injection of therapeutic amounts of rabbit serum correspond to those following the use of horse serum. These are: (a) anaphylactic shock; (b) the accelerated or anaphylactoid reaction; (c) the chill reaction; (d) serum sickness. Only the last two of these reactions will be discussed at this time.

Chill reaction. Considerable work has been done on the factor or factors in salt solution and solutions of foreign protein which cause chill reactions. There is no unanimity of opinion as to whether the chill-producing substances are extrinsic or intrinsic in origin. Although methods employed for removing these substances either by processing or by fractionation and concentration of the serum have not been uniformly successful, progress in this direction has been made.

Not every lot of unconcentrated rabbit serum produces chills. Indeed, in certain cases amounts as great as 200 cc. or even 500 cc. may be injected intravenously in a single dose without producing any thermal reaction whatever. Similarly, the amount of chill-producing substances varies greatly from one lot of rabbit serum to another. Certain lots contain only a small amount, so that 50 cc. or more of serum can be injected intravenously without the occurrence of a chill, whereas the injection of 100 cc. of the same serum may produce a thermal reaction.

If at the time of injection of the larger amount of such relatively non-toxic sera, 0.6 to 0.9 gm. of acetylsalicylic acid is given by mouth, the chill reaction may be entirely prevented. However, this drug is not effective when serum is used containing a higher concentration of the chill-producing factor.

In a search for substances which might relieve the chill reaction, Beeson and Hoagland[17] observed that in about 50 per cent of cases the intravenous administration of calcium chloride would abort almost instantaneously the chills following the injection of rabbit serum. However, this agent is effective in relieving only the milder chill reactions.

Serum sickness. Serum sickness following the administration of rabbit serum has occurred in 65 per cent of cases. This is almost the same incidence of serum sickness as that which we have observed following the use of concentrated horse antipneumococcal serum. The manifestations of serum sickness do not differ from those seen when horse serum is employed.

The use of unconcentrated rabbit antipneumococcal serum in the treatment of pneumonia due to pneumococci of various types has been previously described in two reports from this hospital.[18] In the second paper a number of patients were included who had been treated in other institutions with the same lots of serum. The present report deals only with patients who have been treated in the Hospital of the Rockefeller Institute.

In Table I are shown the results which have been obtained in the treatment of pneumonia in this hospital using unconcentrated rabbit serum.

A total of 100 patients, including infections due to pneumococci of nine different types, has been treated. Eleven patients have died—a mortality of 11 per cent. Of the eleven who died, seven suffered from Type III pneumonia. The final judgment on the efficacy of Type III rabbit antipneumococcal serum has not been made, but in a certain group of patients a beneficial effect has occurred, particularly in individuals before the sixth decade. In such patients a dramatic response may occur, similar to that which is seen so frequently in the serum treatment of Type I pneumonia. Of the patients with Type III pneumonia who died, only three could be considered as having received adequate dosage of serum by our present standards, but the fact that these patients died despite intensive treatment makes it imperative to pursue further the investiga-

TABLE I

MORTALITY RATE IN 100 PATIENTS TREATED WITH UNCONCENTRATED RABBIT ANTIPNEUMOCOCCAL SERUM

Type	*Number of cases*	*Number of deaths*
I	28	1
II	10	2
III	26	7
IV	4	1
V	3	–
VI	2	–
VII	10	–
VIII	9	–
IX	4	–
XIV	2	–
XVIII	1	–
XIX	1	–
Total	100	11 (11%)
Excluding Type III cases	74	4 (5.4%)

tion of the therapy of Type III infections.

Because of the questionable efficacy of Type III serum it seems fair to exclude the twenty-six cases of Type III pneumonia from the series. If this is done, the mortality rate is only 5.4 per cent—four deaths in seventy-four cases of pneumonia. The patients who died, other than those in the Type III group, illustrate what has long been known concerning antipneumococcal serum therapy in general, namely the advantage of early treatment. All but one of these patients were treated late in the disease; in two, empyema was present associated with severe bacteriemia; one patient had meningitis at the time of admission; and the fourth patient was an elderly man with Type II pneumonia, who had consolidation of four pulmonary lobes when admitted to hospital.

A similar experience with rabbit antipneumococcal serum is reported by Loughlin and his co-workers from the Long Island College Hospital.[19] Sixty-nine patients with pneumonia due to Types I, II, V, VII, VIII, and XIV were treated, with a mortality rate of 7.4 per cent.

During the past two years an attempt has been made in each case to administer the required amount of antibody within as short a period as possible. Great assistance has been rendered in this study by using the skin test with the specific polysaccharide of the homologous type as an aid in the control of dosage. Francis[20] showed that when a patient had received an amount of Type I serum sufficient to initiate recovery the intradermal injection of Type I polysaccharide would result in a wheal

TABLE II

DEFERVESCENCE TIME IN TYPE I CASES TREATED WITH HORSE OR RABBIT SERUM

Antipneumococcus serum used	*Method of administration*	*Number of cases*	*Defervescence—average time in hours*
Concentrated horse serum	Divided doses	25	22.6
Unconcentrated rabbit serum	Single and divided doses (all cases)	26	13.8
Unconcentrated rabbit serum	Within two hours	16	9.3

TABLE III

DEFERVESCENCE TIME IN CASES TREATED WITHIN EIGHT HOUR PERIOD

Type	*Number of cases*	*Defervescence—Average time in hours*
I	19	11.1
II	4	6.7
III	5	11.2
IV	3	8.0
V	3	7.3
VI	1	6.0
VII	5	8.6
VIII	5	9.8
IX	2	11.5
XVIII	1	7.0
Total	48	9.75

and erythema reaction at the site of injection. This test has proved a valuable guide to serum dosage with horse and rabbit serum of several types, since on the development of a positive skin test, serum therapy may be safely discontinued.[21]

Table II shows the average time required for defervescence in patients with Type I pneumonia treated with concentrated horse serum, and in patients receiving unconcentrated rabbit serum. With concentrated horse serum, treatment was carried out by the divided dose method, serum being given at two to four hour intervals. Defervescence in these twenty-five cases occurred in an average of 22.6 hours from the beginning of treatment. In twenty-six cases treated with unconcentrated rabbit serum, defervescence occurred in an average of 13.8 hours. However of these twenty-six cases, sixteen received the full therapeutic amount of serum in less than two hours, and in this group defervescence occurred on the average in 9.3 hours.

The same method of intensive therapy has been applied to the treatment of pneumonia due to other types as well. Table III shows the results obtained in forty-eight cases. In many instances the full therapeutic dose of serum was given at one injection shortly after the patient was admitted to hospital. In the remainder, treatment was completed within eight hours. The average time required for defervescence was only 9.75 hours. In practically all of these cases the skin test with the specific polysaccharide was employed to determine when sufficient serum had been given.

The effective amount of rabbit antipneumococcal serum varied from case to case, and at present no definite rules regarding dosage can be stated. We feel that in the adult patient with uncomplicated Type I pneumonia of not more than three days' duration, a dose of 125,000 units should be given as soon as possible. After the third day a somewhat larger initial dose should be given, particularly if the consolidation involves more than one pulmonary lobe, or complications such as bacteriemia are known to be present.

The favorable results which have been obtained in this relatively small series of cases have probably been due in part to the administration of a highly potent serum and in part to intensive treatment controlled by an accurate method for determining the required dosage.

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DEATHS OF FELLOWS

Douglas, John: 568 Park Avenue, New York City; born in New York City August 5, 1875; died in New York City December 5, 1938; received the degree of Bachelor of Science from the College of the City of New York in 1894 and graduated in medicine from the College of Physicians and Surgeons, New York, in 1898; elected a Fellow of the Academy January 5, 1905 and served as Chairman of the Section of Surgery, 1915-16.

Dr. Douglas had been attending surgeon to the St. Luke's Hospital since 1927 and president of its medical board 1932-33; consulting surgeon to the Bellevue Hospital since 1927; consulting surgeon to the Harlem Eye and Ear Hospital since 1929; and consulting surgeon to the Knickerbocker Hospital since 1930. He was an instructor at New York University and Bellevue Medical College, 1904-12, and clinical professor of surgery at New York University since 1912.

Dr. Douglas held a certificate from the American Board of Surgery, and was a Fellow of the American College of Surgeons, the American Medical Association, and a member of the American Surgical Association, the New York Surgical Society and its president, 1931-32; the County Medical Society and its president in 1928; and the State Medical Society. He was an alumnus of St. Luke's Hospital, Bellevue Hospital and Sloane Hospital for Women.

Dr. Douglas was the author of many articles and reports on surgical subjects.

Gottlieb, Mark Jacob: 239 West 75 Street, New York City; born in Montrose, Pennsylvania, in 1885; died in New York City, December 21, 1938; graduated in medicine from New York University and Bellevue Hospital Medical College in 1909; elected a Fellow of the Academy October 5, 1922.

Dr. Gottlieb was associate otolaryngologist to the Harlem Hospital. He was a diplomate of the American Board of Otolaryngology, a Fellow of the American Medical Association and a member of the County and State Medical Societies.

HORN, WALTER LOUIS: 1040 Park Avenue, New York City; born in New York City, March 1, 1891; died in New York City, December 29, 1938; graduated in medicine from Fordham University Medical School in 1916; elected a Fellow of the Academy May 4, 1922.

Dr. Horn was associate otologist to the Mount Sinai Hospital, assistant surgeon to the Manhattan Eye, Ear and Throat Hospital, surgeon director of otolaryngology to the Misericordia Hospital and assistant Otorhinolaryngoligist to the Metropolitan Hospital.

Dr. Horn was a diplomate of the American Board of Otolaryngology, a fellow of the American College of Surgeons, the American Medical Association and a member of the American Academy of Ophthalmology and Otolaryngology, and the County and State Medical Societies.

LOPEZ, JOSE ANTONIO: 220 West 98 Street, New York City; born in San German, Puerto Rico, May 8, 1881; died in New York City, November 19, 1938; graduated in medicine from Syracuse University Medical College in 1904; elected a Fellow of the Academy November 6, 1919.

SUTTON, LUCY DUBOIS PORTER: 168 East 74 Street, New York City; born in Bridgewater, Massachusetts, February 16, 1891; died in New York City, December 23, 1938; graduated in medicine from Cornell University Medical College in 1919; elected a Fellow of the Academy January 6, 1927; elected Secretary of the Section of Pediatrics May 12, 1938.

Dr. Sutton was assistant professor of pediatrics at Cornell University Medical College and associate visiting physician to the Children's Medical Service at Bellevue Hospital.

Dr. Sutton held a certificate from the American Board of Pediatrics and was a member of the American Public Health Association and the American Academy of Pediatrics.